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GOLD SALTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS; A STUDY OF 245 CASES *

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THE use of gold salts in the treatment of rheumatoid arthritis has an interesting and rather unusual history. In 1927 Möllgaard [1] carried out some experiments with gold salts as to their effect on the tubercle bacillus. His results were so interesting that Secher [2] in Copenhagen undertook to treat tuberculosis in man with gold salts. Some of the French students of arthritis had formulated the theory that rheumatoid arthritis was a form of tuberculous joint disease. It was possibly this concept of the problem which led Forestier [3] in 1929 to try gold salts in the treatment of rheumatoid arthritis. About the same time Feldt,[4] Umber,[5] and Zimmer [6] in Germany reported successful results with gold salts in the treatment of arthritis. Early in its career gold therapy met with considerable criticism. As Tegner [7] says: "A disease of unknown etiology was being treated with a drug of unknown action, but of very widely known toxic properties," on the slim assumption that there was a possible connection between tuberculosis and rheumatoid arthritis. However, shortly after the publications by Forestier [3] and the German investigators, Slot and Deville [8] in England confirmed the observations of these writers, and since then a number of important reports have appeared in the English and French literature.

In 1934 Forestier,[9] in his Hunterian lecture, summarized his results with gold therapy in 500 cases of rheumatoid arthritis. In this report he discusses the various forms of gold salts and concludes that for practical purposes gold sodium thiomalate (Myochrysine) and gold thioglucose (Solganal-B) are the most satisfactory agents. Of the 500 cases treated 70 to 80 per cent responded well to gold therapy. Fifty per cent of early cases,

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but only 25 per cent of cases of more than two years' duration, were permanently relieved. In this article Forestier reported his first fatality from gold therapy, a case of agranulocytosis.

In 1935 Hartfall and Garland [10] made their first report on 100 cases of rheumatoid arthritis, nearly all of which had been treated with gold sodium thiosulfate intravenously. The most noteworthy feature of this report was that 45 per cent of the patients had toxic reactions; three patients in the series died, one from agranulocytosis, two from hemorrhagic purpura. One of the deaths from purpura occurred after only five injections of gold salt (total dosage 0.36 gm.). Hartfall and Garland reported either cure or marked improvement in 68 per cent of their cases.

In 1936 Forestier and Certonciny [11] made an interesting study on 50 cases of rheumatoid arthritis who had received at least four courses of gold and who had been observed for at least three years. They divide their cases into a "small dose" series and a "large dose" series (that is, small and large individual doses). In the small dose series, 70 per cent obtained good results. In the large dose series the results were satisfactory in 50 per cent. The authors explain this apparent inconsistency by noting that large doses were usually given only to severe cases. In 64 per cent of this series the results were excellent (cures or near cures). In 28 per cent the results were only fair; in 8 per cent, negative. In the early cases (less than one year's duration), approximately 75 per cent obtained excellent results. Forestier and Certonciny found that the patients who had recovered and had no relapse all showed a normal sedimentation rate after treatment; furthermore, that patients who recovered but later relapsed always showed an increase in the sedimentation rate during the relapse. In this group of 50 cases who had been observed over a period of three years, 46 per cent had relapses.

In 1937 Hartfall, Garland and Goldie [12] published the largest series so far reported in the literature, a study of 750 cases of rheumatoid arthritis, all of whom received gold therapy. These authors used the commoner gold salts now on the market, but found nothing to choose between them so far as therapeutic value was concerned. However, because of the trouble which they had encountered in their earlier study, they reduced the total dosage of gold salt from 2 gm. to 1 gm., and gave the patients a rest interval of three months between courses. In this large series of cases, the authors obtained either cure or marked improvement in 66.7 per cent of the cases. Relapses occurred in 21 per cent of the series; 41.9 per cent had toxic reactions. The latter were severe, however, in only 6 per cent. In this study there were seven deaths (0.78 per cent) due to gold salts; three due to hemorrhagic purpura; one due to agranulocytosis; two due to subacute necrosis of the liver; and one due to exfoliative dermatitis.

In 1937 Copeman and Tegner [13] stated that of 51 cases of rheumatoid arthritis treated with gold salts, 58 per cent were cured or greatly improved, whereas 18 per cent showed slight or moderate improvement.

In 1938 Ellman and Lawrence [14] reported a carefully controlled series of 52 cases of rheumatoid arthritis, 32 of whom were treated with Solganal-B Oleosum, whereas 20 received only injections of almond oil. These authors reported one fatality from hemorrhagic purpura with associated agranulocytosis. They insisted that toxic reactions were most likely to occur in patients with a normal sedimentation rate. They advised, therefore, only small doses of gold when the sedimentation rate reaches normal. In a follow-up study published in 1940, Ellman, Lawrence and Thorold [15] reported on 90 cases, which they divided into three groups of 30 each. One group received Solganal-B in doses of 0.2–0.3 gm. weekly. The second group received 0.1 gm. weekly of Solganal-B. The third group received only sterile almond oil. Treatment was continued for a period of nine months in each case. Of the cases treated with large doses of gold, 47 per cent became inactive within nine months. Of those who received small doses, 27 per cent became inactive. In the control series only 3 per cent became inactive. By "inactive" the authors meant freedom from joint pain and a normal sedimentation rate. These authors again stressed the importance of the sedimentation rate as a guide to treatment and claimed that out of a total of 25 cases of gold intoxication, 96 per cent occurred in the presence of a normal sedimentation rate. Recurrence was not encountered among patients in whom the disease had been rendered completely inactive.

In America there has been comparatively little published on the subject of gold therapy in rheumatoid arthritis. In 1939, however, two articles appeared, one by Key, Rosenfeld and Tjoflat,[16] and the other by Snyder, Traeger and Kelly.[17] Key and his co-workers gave myochrysine to 70 patients with arthritis, 53 of whom were rheumatoid cases. Of the 70 cases, 44 had toxic reactions, but there were no deaths. In the 53 cases of rheumatoid arthritis treated with gold salts, 20 (38 per cent) were either arrested or showed marked improvement. These authors consider gold salts particularly valuable in early cases.

Snyder, Traeger and Kelly [17] treated 50 cases of rheumatoid arthritis with gold salts but obtained satisfactory results in only 12 per cent of the cases. These figures are quite at variance with those reported by most other investigators.

Physiological Effects of Gold

The mechanism by which gold salts act in rheumatoid arthritis is not understood. A number of theories have been proposed. Kling, Sashin and Spanbock [18] thought that the bactericidal effect of gold salts was negligible. They found that in experimental animals gold is deposited in high concentration in the synovial membrane, and they concluded that the efficiency of gold salts in rheumatoid arthritis is probably due to the stimulation of the general reticuloendothelial system, as well as to the effect of the local deposit of gold on the defense mechanism of the synovial membrane. Feldt [4]

thought that in acute and chronic infections the most effective gold compounds were those which contained a sulfur radicle. With such agents he was able to control syphilis in rabbits with an efficiency equal to that of salvarsan.

More recently, Dawson and Hobby [19] have shown that gold salts possess marked chemotherapeutic properties against hemolytic streptococcal infections in mice. The authors remark that the effect was comparable to that obtained with the sulfonamide derivatives. Gold sodium thiomalate had a marked bacteriostatic effect in vitro against the *Streptococcus hemolyticus* at a 1 : 10,000 dilution.

Sabin and Warren [20] have studied the effect of gold compounds on experimental arthritis in mice, which they produced by intravenous injection of pleuropneumonia-like organisms. Various gold salts were found to exert a definitely curative effect on this disease, and the earlier the treatment was begun, the more complete and rapid was the therapeutic response.

Rothbard, Angevine and Cecil [21] have investigated the effect of gold sodium thiomalate on experimental hemolytic streptococcal arthritis in rats. In this study the authors found that gold sodium thiomalate is an effective chemotherapeutic agent in the prevention of arthritis produced by the hemolytic streptococcus, but that it does not cure the disease once it is established.

Some interesting studies have recently appeared on the fate of gold when injected into the human body. Freyberg, Block and Levey [22] injected various gold salts into human subjects and studied their rate of absorption and excretion. These authors found that about 75 per cent of gold was retained in the body during a course of gold therapy, whereas the other 25 per cent was excreted for the most part through the urine, a small fraction through the feces. The gold salt continues to be excreted for weeks, even months, after the injections have been concluded. The authors suggest that the slow excretion of gold salts may explain the serious toxic effects which they sometimes produce on various organs.

Hartung [23] has recently shown that subcutaneous injections of gold salts are followed by a marked increase in the bacteriostatic power of the patient's serum against the hemolytic streptococcus. These effects are in direct proportion to the amounts of gold administered. In view of the demonstrated bacteriostatic power of gold salts, one would naturally expect the serum of treated patients to possess this quality.

Present Study

The senior writer of this report began working with gold salts in the treatment of rheumatoid arthritis in 1933, shortly after the visit of Forestier to this country. We had treated only a few cases, however, before we ran into trouble in the form of a severe exfoliative dermatitis. This experience cooled our enthusiasm somewhat, but we continued using gold salts on

selected cases during the following five years. In 1938 we began to use gold intensively, and during the past three years practically all of our rheumatoid cases have received gold therapy.

The present study includes 245 cases of rheumatoid arthritis, all of whom received gold salts. Ten cases of ankylosing spondylitis have been excluded from some of the tables because we felt that they should be considered separately. In this study we have made a particular effort to include only cases of *bona fide* rheumatoid arthritis. Seventy per cent of the patients in the series showed one or more fusiform fingers, and of the remainder practically all presented swollen knuckles, ankyloses or deformities, or other characteristic features of the disease. Of 76 patients who had roentgen-rays of the joints, 80 per cent showed the characteristic radiographic changes. Ninety-five per cent of the series presented an elevated sedimentation rate. Sixty-four per cent of 193 patients gave a positive agglutination reaction to the *Streptococcus hemolyticus*. Eighteen patients, or 7.6 per cent, had one or more subcutaneous nodules. A number of patients who had received gold therapy were finally excluded from this study because of some doubt in our minds as to their clinical identity.

Ninety-two patients were studied in the out-patient department or in the wards of the New York Hospital. The remaining 153 were private patients. Both series, however, received the same work-up and laboratory study. As far as we can see, there is not much difference in the type of patient which one sees in the clinic and in private practice.

Age and Sex. This series contained about twice as many females as males (158 vs. 87). The age at onset fell between 20 and 40 years in 40 per cent, and between 40 and 60 years in 43 per cent of the cases.

Degree of Severity. We classified our rheumatoid arthritics according to severity into four groups, as follows:

Group 1. (1 +.) Mild cases, ambulant. These patients were still able to work every day and had only a moderate degree of swelling and pain in several joints, including usually two or three fingers. Twenty-nine per cent of the patients studied fell into this group.

Group 2. (2 +.) Moderately severe cases, mostly ambulant. Great majority of more than a year's duration. These patients were usually only partly incapacitated and could do certain kinds of work. They invariably presented a multiple arthritis with well established changes in the hands, wrists, knees and other joints. This was our largest group, constituting 57 per cent of the total series.

Group 3. (3 +.) Severe cases, only partially ambulant. Many of these patients were treated as bed patients during part of the period of observation, either in the home or in the New York Hospital. Thirteen per cent fell into this group.

Group 4. (4 +.) Very advanced type of rheumatoid arthritis, totally crippled, unable to walk. There were only two cases of this type included in the series.

Our material is also classified according to the duration of disease. All patients were divided into early and late cases, early cases being those who had had arthritis not more than one year, late cases being those who had had arthritis for more than one year. The late cases outnumbered the early cases by almost three to one (170 to 65).

Ten patients in the series presented the picture of ankylosing spondylitis of the Marie-Strümpell type.

Two cases occurred in children under 10 years of age and were classified as Still's disease. It is now generally recognized, however, that Still's disease is nothing more than juvenile rheumatoid arthritis.

Associated Diseases. Of our cases 4.2 per cent had psoriasis combined with arthritis and showed the characteristic changes in the finger nails and terminal phalanges.

Eight cases presented the typical signs of rheumatic heart disease. It should be added, however, that because of the chronicity of the joint changes we felt justified in classifying them as rheumatoid arthritis rather than as subacute or chronic rheumatic fever.

Other Forms of Therapy. The great majority of patients in this study had had arthritis for a number of years and had tried various forms of therapy, usually without any permanent benefit. The agents that had been most frequently employed were vaccines, vitamins, sulphur, physiotherapy, and removal of foci of infection.

Methods

Laboratory Methods. A complete blood count and urinalysis on patients who were receiving gold therapy were carried out once a month for signs of intoxication. The sedimentation rate of the red blood cells, as determined by the Rourke and Ernstene method, was determined before treatment was started and was repeated every two to three months while gold was being administered. In a few patients frequent platelet counts were made, but they afforded little or no information. The streptococcus agglutination test was made in the majority of instances. In many cases in which the diagnosis was in doubt, roentgen-rays of the joints were taken.

Method of Treatment

The present study is concerned primarily with the effect of gold salts on the course of rheumatoid arthritis. However, supplementary therapy in the form of vitamins, physical therapy and streptococcus vaccine was used in certain instances. In evaluating results, however, these forms of treatment were not taken into consideration inasmuch as they have usually been found ineffective in this disease when used either singly or in combination.

With respect to gold salts, we have used only three in this study.*

*We are indebted to Merck & Company, Schering Corporation and Abbott Laboratories for the gold salts employed in this study.

1. Gold sodium thiomalate—$C_4H_3O_4SAuNa_2$—(Myochrysine)—207 cases.
2. Aurothio-glucose—$C_6H_{11}O_5SAu$—(Solganal-B Oleosum) — 40 cases.
3. Gold sodium thiosulfate—$Na_3Au(S_2O_3)2H_2O$ — 3 cases.

There were a few instances in which the same patients received both myochrysine and Solganal-B. Myochrysine and Solganal-B were administered intramuscularly into the buttock. Gold sodium thiosulfate was given intravenously. In all cases the gold injections were administered once a week.

Dosage. The usual plan was to start the patient on 10 mg. of the gold salt and work the dose up gradually to 50 or 100 mg. Occasionally patients who did not respond to these doses were given 200 mg. injections, but this was exceptional.

Our material can be roughly divided into two groups: (1) Large dose series, in which the patient received weekly injections of 100 mg. of gold salt until he had taken 1–1.5 gm. of the drug. There were 151 cases in this group. (2) Small dose series. The maximum dose in this series was 50 mg. administered once a week. These patients received a total of .5–1 gm. of gold salt. The number of cases in this group was 63. A small group of 11 patients received a mixture of small and large doses. These figures do not include 38 patients who received inadequate treatment nor the 10 cases of ankylosing spondylitis.

Total Dosage of Gold. Most writers on gold therapy have advocated the administration of gold in courses, each course to consist of a total dosage of 1 to 1.5 gm. Most patients require at least two courses, and many have to have four or five, or even more.

In our investigations on gold therapy we followed the usual rule of allowing an interval of six to eight weeks to elapse between courses of gold therapy. However, in the cases of patients who developed toxic reactions gold was immediately discontinued, sometimes temporarily, sometimes permanently.

In table 1 we have classified our cases according to total dosage of gold salts. Forty-one, or 16 per cent, of our patients received a total dosage of less than 0.5 of a gram, which we considered inadequate therapy. Not all of these discontinued gold, however, on account of an intolerance for the drug, as will be pointed out later.

TABLE I

Total Dosage of Gold Salts in 245 Cases of Rheumatoid Arthritis

Amount	Cases	Per Cent
Less than 0.5 gm.	41	17
0.5–0.9 gm.	63	26
1.0–3.0 gm.	116	47
Above 3.0 gm.	19	8
Amount Questionable	6	2
Total	245	

In table 2 our cases are classified according to the number of courses of gold therapy which they received. The number can be roughly divided between 107 who received only one course, and 90 who received two or more courses. It should be added that many of the patients who are listed in this

TABLE II

Courses of Gold Salts in 197 Cases of Rheumatoid Arthritis *

Number of Courses	Cases	Per Cent
One	107	54
Two	53	27
Three or More	37	19
Total	197	

* 38 cases of inadequate treatment excluded. 10 cases of ankylosing spondylitis excluded.

table as having only one course are now receiving their second or third course. Most authorities have insisted that every patient, no matter how successful the results with the first course of gold, should receive at least two courses to prevent a possible relapse.

RESULTS OF TREATMENT

The authors have devoted a good deal of thought to the question of how the results should be classified. We finally adopted in part the terminology of Ellman and Lawrence, who described those patients who became free of all swelling and pain as "remissions." The term "inactive" would be equally applicable. To speak of a "cure" would be unsuitable because, as in the case of tuberculosis, a considerable number of arthritics relapse. On the other hand, we think it is a mistake to follow the terminology used by certain European writers and speak of these apparently cured cases as "greatly improved," a term which does not adequately describe their status. We have, therefore, decided to classify our cases as follows:

(1) Remissions. Patients who become free of all pain and swelling, although they may have some residual deformities, such as one or two ankylosed fingers, and who are again able to do a full day's work. Most patients in this group have a normal or only slightly elevated sedimentation rate at the time of their remission.

(2) Greatly Improved. Patients who still have some swelling and pain, but are able to work for at least part of the day. Sedimentation rate usually reduced, but not often normal.

(3) Moderate Improvement. The patients in this group show some improvement from gold treatment, but the results are not convincing. The improvement is of the type which any arthritic might undergo spontaneously.

(4) No Improvement.

In table 3 the gross results of treatment with gold salts in 235 cases of rheumatoid arthritis are listed. Thirty-one per cent of those receiving adequate therapy had a complete remission with respect to pain and swelling in

TABLE III

Results with Gold Therapy in 235 Cases of Rheumatoid Arthritis *

Result	Cases	Per Cent
Remission	62	31
Greatly Improved	68	35
Moderately Improved	39	20
No Improvement	28	14
Total	197	
Insufficient Treatment	38	
Total	235	

* 10 cases of ankylosing spondylitis excluded.

the joints. Thirty-five per cent showed marked improvement. Combining these two groups, 66 per cent either became inactive or were greatly improved. This figure checks closely with the 66.7 per cent of Hartfall and Goldie and the 68 per cent of Forestier, who showed either remission or marked improvement. The remaining third of the cases were either only moderately improved or showed no improvement at all.

In table 4 we have summarized the results of gold therapy in relation to the duration of the arthritis. This table indicates the advantage of gold therapy early in the disease. Thirty-nine per cent of the cases treated early

TABLE IV

Results with Gold Therapy in Relation to Duration of Arthritis

Result	Early Cases	Late Cases
Remission	20 (39%)	42 (29%)
Greatly Improved	20 (39%)	48 (33%)
Moderately Improved	5 (10%)	34 (23%)
No Improvement	6 (12%)	22 (15%)
Total	51	146
Insufficient Treatment	13	25
Total	64	171

had remissions as compared with 29 per cent of the late cases. Thirty-nine per cent of the early cases showed great improvement as compared with 33 per cent of the late cases. Altogether, 78 per cent of the patients treated early showed either complete remission or great improvement.

When the results of gold therapy were analyzed in relation to the severity of the disease, the percentage of remissions and great improvement were found to be just about the same in the mild and in the severe cases, namely 63

versus 67 per cent. However, these figures are not as inconsistent as they might at first appear. It has long been recognized that the severe fulminating type of arthritis often responds better to treatment than the comparatively mild, indolent form.

A further analysis of the remissions indicates that 77 per cent of them had a total of one gram or more of gold salt, whereas only 41 per cent of those who showed no improvement had a total dosage of one or more grams.

In this connection it is interesting to analyze the 38 cases who had insufficient treatment with gold salts. We were curious to know how many of these patients stopped the treatment because of reactions and how many for other less important reasons. The following figures throw some light on this question.

Of the 38 cases who received inadequate gold therapy, 19, or 50 per cent, discontinued the treatment because of toxic reactions. Nine stopped because of failure to show immediate improvement. The two cases of juvenile rheumatoid arthritis received only small doses of gold, and in the eight remaining cases the cause for discontinuance could not be determined. We wish to stress one point, however, and that is that many patients, even those who have had severe reactions, can, after a sufficient rest period, take further gold treatment without any complications. In such patients, however, it may be wise to limit the maximum individual dose to 25 or 50 mg.

Ankylosing Spondylitis. We have treated 10 cases of ankylosing spondylitis with gold salts. Three received inadequate treatment. Of the remaining seven there was only one patient who improved. This type of arthritis appears to be refractory to gold treatment.

Still's Disease. Two children with Still's disease were treated with gold salts. Because of their age, small doses (not over 25 mg.) were used and the total dosage was not carried above 0.5 gm. One child had a complete remission following gold therapy, which has lasted over five years. The other child is still under treatment and has shown moderate improvement. In this latter case it was necessary to interrupt treatment because of a tendency to thrombocytopenia. However, she was subsequently able to tolerate small doses of gold satisfactorily.

Effect of Gold Treatment on the Sedimentation Rate. Much has been written concerning the effect of gold therapy on the sedimentation rate, and all are agreed that in patients who respond well to gold therapy, the sedimentation rate is reduced and in many cases actually reaches normal. As mentioned above, 95 per cent of our patients showed an elevated sedimentation rate before gold treatment was instituted. In the group of patients who had remissions after gold therapy, 47 per cent of those with a high sedimentation rate developed a normal or only moderately elevated sedimentation rate. In contrast to this group, of those who showed no improvement under gold therapy, only 5 per cent with a high sedimentation rate showed a striking reduction after gold therapy. If one includes only those patients whose sedimentation rate actually reached normal, the contrast is even more striking;

37 per cent of the patients in the remission group developed a normal sedimentation rate after gold treatment, whereas not a single case in the "no improvement" group developed a normal sedimentation rate after treatment.

We have not been able to determine the factors which are essential in obtaining a remission. All we can say from a survey of our material is that a majority of the patients who had remissions were treated early, received a larger total dosage of gold, and showed a rather rapid drop in the sedimentation rate. It is also interesting to note that 53 per cent of the remissions had some form of toxic reaction to gold, as compared with 42 per cent for the entire series. Age, sex and severity of the disease do not appear to be determining factors.

Relapses. Comparatively little has so far appeared in the literature on gold therapy concerning the prevention and treatment of relapses. Unfortunately, relapses are quite a common occurrence and detract a great deal from the efficiency of gold therapy. In table 5 we have indicated the incidence of relapses in patients treated with gold salts. Thirty-four per cent of the remissions, and 50 per cent of the "greatly improved" patients relapsed. Most relapses come on within six to 12 weeks after gold therapy has been discontinued. We have seen relapses occur, however, as late as one or two years after remission. There is general agreement among writers on gold therapy that relapses are milder than the original attack. The symptoms usually reappear in the same joints and are most likely to occur in patients whose sedimentation rate remains high in spite of striking improvement.

TABLE V

Incidence of Relapse after Treatment with Gold Salts

Result of Gold Therapy	Cases	Relapses	Per Cent
Remission	62	21	34
Greatly Improved	68	34	50
Moderately Improved	39	13	36

Our investigations indicate that the great majority of patients get the maximum benefit of gold therapy from the first course. Many of those who relapsed again showed remissions or great improvement after further treatment, but improvement was rarely more marked than with the original course of gold treatment. Fifty per cent of the remissions who relapsed became inactive again after further gold therapy, and 66 per cent of the greatly improved group who relapsed were greatly improved once more by a second course of gold therapy. Only two patients in the greatly improved group who relapsed had a remission following the second course of gold therapy! In the moderately improved group there were 13 relapses, and further gold treatment did not elevate any of these patients into the remission or greatly improved groups. However, our statistics indicate that a considerable percentage of patients who relapsed again had remissions or great improvement following a second course of gold treatment, for in the final

analysis 50 per cent of our cases, in spite of relapses, achieved a successful result, i.e., either a remission or great improvement.

Duration of Remissions. In table 6 we have indicated the duration of remissions following gold therapy up to the time of the conclusion of our

TABLE VI

Duration of Remissions in 50 Cases of Rheumatoid Arthritis Treated with Gold Salts

Duration of Remission	Number of Cases	Per Cent
Less than 6 Months	10	20
6 Mos.–1 Year	14	28
1–2 Years	16	32
2–5 Years	8	16
Above 5 Years	2	4
Total	50	

experiment on February 1, 1941. It is interesting to note that in this table remissions have lasted more than a year in 52 per cent of the cases.

Toxic Reactions. These reactions are listed in table 7. The incidence of toxic reactions was 42 per cent, a figure which checks closely with that of

TABLE VII

Toxic Reactions to Gold Salts in 245 Cases of Rheumatoid Arthritis

Exfoliative Dermatitis	11
Other Skin Lesions	52
Stomatitis	13
Gastrointestinal Symptoms	18*
Jaundice	2
Purpura	3
Agranulocytosis	1
Bronchitis	2
Albuminuria	3
Total	105

* One case of ulcerative enteritis died.

some of the preceding studies. In estimating the number of toxic reactions we have not included the immediate nitritoid reactions which we obtained with certain lots of myochrysine and which now, fortunately, have been eliminated. In this table we have placed exfoliative dermatitis first because it is the most prevalent of the severe reactions. As a matter of fact, in those patients who had localized exfoliative dermatitis, the condition was not severe, but quite uncomfortable. Four patients, however, with generalized exfoliative dermatitis had to be hospitalized. It is interesting to observe that four out of our 11 cases of exfoliative dermatitis developed a rash after a total dosage of less than 0.5 gm. of gold salts. Of the patients who developed exfoliative dermatitis, nearly all showed marked improvement in their arthritis during and following the dermatitis, although some relapsed later.

The next most common skin lesion was *squamous dermatitis.* This usually cleared up fairly promptly after discontinuance of gold.

Other less frequent skin lesions were erythema, herpes zoster, herpes labialis, folliculitis, dermatitis pigmentosa and furunculosis.

Stomatitis was fairly common but rarely caused the patient much annoyance. A few patients lost their sense of taste for a short time.

Gastrointestinal symptoms were usually mild, consisting of nausea, colicky pains and diarrhea. One patient, aged 70, following her first injection of myochrysine, developed an ulcerative enteritis (confirmed by autopsy) from which she eventually died. We were not convinced, however, that this patient's death should be attributed to the gold injection. In the first place, she had had symptoms of intestinal trouble for years. In the second place, she had received only one injection of 25 mg. of myochrysine. There is no record of anyone's developing a fatal gold intoxication from such a small dose of gold salt.

Two patients in our series had jaundice but both made an uneventful recovery. It was interesting that both of these patients had a temporary remission of their joint symptoms during, and for a few months following their attack of jaundice, thus corroborating the observations of Hench and others that jaundice is frequently followed by a temporary cessation of arthritic manifestations.

Three of our patients developed purpura, but this cleared up promptly when gold was discontinued. Two out of the three cases of purpura occurred after less than 0.5 gm. of gold. One patient had an agranulocytosis, accompanied by intense angina, but recovered.

"Gold bronchitis" occurred twice, marked albuminuria in three cases. One of the patients who developed albuminuria showed many granular and hyaline casts, but this eventually cleared up almost entirely, and there was no evidence of impaired renal function.

We have been unable to determine what factors are responsible for toxic reactions in some patients and not in others. Furthermore, we have found no effective means of prevention or treatment.

Discussion

Joseph Miller's famous remark about "the inevitable 70 per cent" of rheumatoid patients who improve under almost any kind of treatment has been much quoted. Spontaneous remissions, of course, do occur in rheumatoid arthritis, but they have been extremely rare in our experience and the patient may have to wait several years for the remission. Gold therapy will sometimes induce a remission in as short a period as six weeks.

Forestier and Certonciny [11] say that only 1 to 2 per cent of true rheumatoid arthritics make a spontaneous permanent recovery. Remissions, however, even a year or more in duration may occur in 10 per cent of cases. They dispute the statements of Dawson, Bauer and others that 15 per cent of

rheumatoid patients make a complete recovery regardless of treatment. This disagreement indicates the great need for a careful follow-up study, over at least a 10 year period, of patients with rheumatoid arthritis.

Dosage is still an unanswered problem as far as gold therapy is concerned. Sabin and Warren [20] found in their studies on experimental arthritis that a better response was obtained with larger doses of the gold compounds. Freyberg and his colleagues believe that the doses which most clinicians use today are unnecessarily large. He bases this opinion on the fact that only a comparatively small amount of the gold injected each week is excreted from the body. It is interesting to note that Secher,[2] one of the first clinicians to work with gold, used very large individual doses, sometimes equal to the total dosage at the present time. Forestier [24] states that of patients who received a total of less than one gram of gold salts, 50 per cent obtained poor results. In our study, we have found that the best results were obtained in patients who received a relatively large total amount of gold salts (1 gram or more). On the other hand, the size of the individual dose did not have a very definite effect on the results of treatment.

Of one thing we are quite convinced, namely, that gold salts are most effective in the treatment of early cases. We are, therefore, in disagreement with Snyder and his co-workers,[17] who say that gold treatment should be undertaken only when the arthritis is refractory to every other form of treatment.

Most authorities believe that a rheumatoid patient should have at least two courses of gold therapy before a decision can be made as to the value of the treatment for that particular patient. Forestier [25] states that patients who receive only one series of gold salts will nearly always relapse. He even goes so far as to say that he never saw a permanent cure result from one series of injections. We find ourselves somewhat sympathetic with this point of view; however, we certainly have the impression quite strongly that if the patient receives no benefit at all from his first gold series, he is not likely to obtain a striking result from a second or third course.

Of all the laboratory tests, the sedimentation rate is perhaps the most important as a check on treatment, although monthly blood counts and urinalyses are important as a means of detecting incipient toxic reactions. Forestier [25] believes that every patient treated with gold should have a coagulation time and a bleeding time before treatment is started, as this would give warning of any tendency toward purpura. However, we are not convinced that this is true.

We agree with Hartfall, Garland and Goldie [12] that although the sedimentation rate is an important guide to treatment, one occasionally sees marked clinical improvement without a drop in the sedimentation rate. Such patients, however, are very apt to relapse a few weeks or months after gold treatment is discontinued. Forestier and Certonciny [11] advise that gold treatment should not be stopped as long as the sedimentation rate is high, but this rule cannot be followed literally.

After a number of years' experience with gold therapy we are disposed to look upon the relapse as just as much of a bugbear to successful treatment as are the toxic reactions. To be sure, the relapse is usually milder than the original attack, but on the other hand it does not seem to yield so strikingly to gold therapy as does the first attack. In the present study more than 52 per cent of remissions lasted longer than a year, and a few have lasted even five years.

The physician cannot be too careful in watching for the early signs of toxic reaction. The longer one works with gold, the less difficulty he seems to encounter with toxic manifestations, probably because he learns from experience how to adapt dosage to the particular case and to take heed of the first premonitions of intoxication.

Judging from the literature, the most serious complication of gold therapy is hemorrhagic purpura. This is a rare complication, but its possibility should be always in mind and the number of platelets noted with every blood count. Gasking [26] has pointed out that for a few days after each injection of gold the blood platelets show a sharp but temporary drop. When gold is given only once a week, the platelet count returns to normal before the next injection of gold, except when the patient is intolerant to gold. Gasking goes so far as to say that a platelet count should be made before each injection of gold.

We agree with Tegner [7] in doubting the value of the various agents which have been recommended for the prevention of toxic reactions. An analysis of our toxic reactions would indicate that although the incidence is high, less than 10 per cent of the patients treated by us with gold salts had to discontinue gold therapy permanently because of intolerance to the agent.

In view of the fact that gold is a dangerous form of therapy, the question may well be asked: "Is it too dangerous to be used by the general practitioner?" The answer to this question must be qualified. Boots [27] advises those who would administer gold salts first to obtain some experience in an arthritis clinic, where gold is being used extensively. This is sound advice, but unfortunately such a procedure is not always feasible. Important things to remember are: (1) Use gold only in cases with typical rheumatoid arthritis. (2) Do not give gold to a patient with a history of previous hemorrhagic disease or with any other serious constitutional disease. (3) Start with small doses and work up gradually. (4) Examine the patient carefully every week for skin rash, sore mouth, etc. (5) Examine the blood and urine once a month.

It has been said by more than one writer that gold is the best single agent for the treatment of rheumatoid arthritis. This does not seem to us a sensational statement, especially when one considers how disappointing most other forms of treatment are. Furthermore, there is no reason to believe that gold therapy has reached its maximum efficiency. Sabin [28] has recently shown that calcium gold thiomalate is much less toxic for animals than the sodium salt. Eventually some such agent may prove to have all of the

therapeutic value of the present products, with much less toxic quality. It seems reasonable to assume that improvements in the product itself, together with more accurate knowledge concerning the dosage, metabolism and excretion of gold, will enable us to use this agent much more efficiently in the future.

Summary

1. In the present study of 245 cases of rheumatoid arthritis, gold salts when given in adequate dosage caused remission or marked improvement in 62 per cent of the cases. In 10 cases of ankylosing spondylitis, gold salts were beneficial in only one case.

2. Even better results were obtained in arthritics of less than one year's duration.

3. The incidence of toxic reactions was high. They manifested themselves chiefly as dermatitis or stomatitis. There was one fatal case of ulcerative enteritis in this series of cases which possibly may have been due to gold salts.

4. Relapses occurred in 42 per cent of the patients who received marked benefit from gold therapy. The relapses were usually milder than the original attack, but yielded less promptly to gold therapy.

5. Gold therapy can be a dangerous form of treatment and requires close observation of the patient and frequent examination of the blood and urine. In spite of its dangers, however, its beneficial effect on the course of rheumatoid arthritis would seem to justify its use in patients who can tolerate the drug.

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THE MANIFESTATIONS IN THE SKIN AND MUCOUS MEMBRANES IN DERMATOMYOSITIS, WITH SPECIAL REFERENCE TO THE DIFFERENTIAL DIAGNOSIS FROM SYSTEMIC LUPUS ERYTHEMATOSUS *

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In dermatomyositis characteristic eruptions are encountered in the skin and mucous membranes. These appearances must always be correlated with the remainder of the clinical picture, yet recognition of them often enables the observer to gain proper orientation in what seems to be an obscure case. Knowledge of these various manifestations provides a more substantial background for an evaluation of the differential diagnosis, therapy and prognosis of a disease that is far more common than the reports in the literature would indicate.[1] Throughout this communication stress will be laid on clinicopathologic correlations and special reference will be made to the differential diagnosis from systemic lupus erythematosus, a disease that is often confused with dermatomyositis.

For convenience the eruptions observed in dermatomyositis may be classified under the following headings:

1. The characteristic appearances that possess diagnostic importance of more or less significance. These may be subdivided, further, into two groups:

a. the lesions that seem to occur independently of the pathologic changes in the muscles and subcutaneous tissues. The net effect produced by these manifestations is that of an exanthematic disease. Under this heading the enanthem as well as a number of "vasomotor" phenomena will also be mentioned.

b. the lesions that are related to or are associated with underlying involvement of the muscular and subcutaneous tissues. Generally speaking, these manifestations seem to fall in the category of "collateral inflammatory changes."

2. The dermatoses that show banal or nondescript attributes; for example, "erythema multiforme," vesiculo-bullous elements, purpura, etc. Their occurrence may tend actually to confuse the clinical picture and, whereas they are best remembered for their negative attributes, there are occasional instances in which these prove to be a "revealing" or directing sign.

Any one of these manifestations may be the initial or, at least, an early sign in dermatomyositis.

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1*a. Eruptions Independent of Underlying Muscular Disease: the Exanthem and Enanthem.* The sites affected most commonly are the face (eyelids, contiguous parts of the forehead and cheeks, including the "flush area"), ears, oral mucosa and the skin overlying the articulations, especially of the small joints of the hands. Of these the eyelids and the small articulations are the most important sites for diagnosis. Often other parts of the body are affected, such as the V-shaped area of the neck and the nuchal region. In some instances the eruption is generalized ab initio or there is gradual spread over the cutaneous surfaces. As a rule, the palms and soles are spared. In cases with widespread involvement of the skin it is the rule that only a few areas show acute or active alterations, and this is especially true in instances in which the original sites of lesions have disappeared or have been replaced by faint pigmentation. Frequently these lesions seem to pursue a fairly chronic course in the sense that they or their sequelae may remain visible a long time, but exceptions do occur. The attributes displayed by the manifestations falling in this group often vary with the stage of the general disease (acute, subacute, chronic), but there are no absolute rules in this respect owing chiefly to the considerable overlapping of stages (for example, an acute exacerbation during apparent clinical quiescence). In particular, the atrophic lesions to be described afford valuable diagnostic evidence of this disease, notably in its chronic forms (chronic dermatomyositis, some cases of myositis fibrosa, etc.).

In dark-hued persons and in negroes the cutaneous manifestations are perhaps less easily recognized; yet the difficulties are generally more apparent than real, for the clinical picture is usually distinctive.

There are, as a rule, no subjective complaints. Itching or burning of the skin of the face, neck and other parts may occur sometimes, and this may occasionally become intense, either spontaneously or following exposure to sun. In some patients the complaint may be severe enough to interfere with sleep. In rare examples scratch marks may be found. Petges [2] stressed the high incidence of pruritus in poikilodermatomyositis, a disease which in my opinion represents a variant of ordinary dermatomyositis. This symptom has no genuine differential diagnostic weight, for it may also occur in systemic lupus erythematosus.

(*a*) *Eyelids.* The appearances exhibited by the eyelids are of capital importance, for in the average example of dermatomyositis these parts are often the first to be affected, frequently as a solitary cutaneous sign. As a rule the lids, especially the upper ones, are swollen and colored a rose pink. Careful inspection reveals that the rosy hue is caused by the presence of numerous closely set telangiectases. The edematous infiltration of these parts is generally of the loose type, and the lower eyelids often hang in folds. In other instances, either early or later in the course, there is a firm edema, and sometimes this is spoken of as lardaceous. Occasionally the tissues pit on pressure, sometimes they are tender to touch. The observation of this inflammatory type of edema has occasionally led some observers to suspect the

possibility of dermatitis venenata; for example, occupational dermatitis, poison ivy, etc.

The edematous lids may recall the appearance in glomerulo-nephritis, but this belief is usually dispelled by the collateral evidence of abundant telangiectases and by the absence of renal damage of a severe type in dermatomyositis, except in rare instances. The association of swollen eyelids and muscle pains produces a striking similarity to trichinosis, hence the old name pseudotrichinosis, but, again, the collateral evidence of an inflammatory reaction in the lids (erythema, telangiectasia, pigmentation) provides the differential feature. I have not seen, thus far, the occurrence of subconjunctival hemorrhages in dermatomyositis, a phenomenon more apt to occur in trichinosis, occasionally in glomerulonephritis in the period of azotemia. The other features of trichinosis need not be discussed, but it must be stressed that the differential diagnosis between this disease and dermatomyositis presents difficulties only in the early acute stage. Chronic dermatomyositis shows a vastly different clinical picture. When there is intense edema of the lids with relatively little or unrecognized telangiectasia, angioneurotic edema may be simulated, but the latter is generally more transitory, lacks the evidence of local inflammatory reaction and shows no systemic manifestations of a similar nature, aside from occasional abdominal pain owing to an entirely different cause. In some instances of dermatomyositis it may be essential to spread the lids apart with the object of rendering the skin taut, before telangiectasia in small patches is discovered, for the latter may be obscured by the overhanging folds. In occasional cases of sinusitis edematous areas may be found near the eyes, but close examination shows that the maximum intensity of this process lies close to or at the root of the nose, with lesser involvement as the eyelids are approached. Twice I have encountered such examples of sinusitis accompanied by myalgic pains, and the resemblances to dermatomyositis were further enhanced by the presence of isolated telangiectatic vessels seen chiefly about the nose. The latter manifestation is not uncommonly encountered in chronic sinusitis, and in some cases there may occur, as a later phenomenon, a pure telangiectatic rosacea showing a violaceous hue, possibly the result of passive congestion in the blood vessels in the nose. The cutaneous manifestations occasionally associated with an ophthalmic vein phlebitis are generally differentiated with ease from those in dermatomyositis. The nearest approach to the eyelid and facial lesions in dermatomyositis I once saw in a woman who had swallowed a fishbone that lodged in a pharyngeal pocket behind one tonsil. In this case the constant gagging caused an erythematous and telangiectatic eruption on the face, eyelids, etc. Finally, puffy red eyelids may be seen in persons who have been weeping excessively.

In the later stages the eyelids in dermatomyositis may be sites of a dense or a reticulated form of pigmentation. In the former case this may be so intense as to suggest the possibility of a phenolphthalein eruption, whereas in the latter instance the picture of poikilodermatomyositis is produced. In occasional examples a degree of thickening of the skin of the lids may be

found, simulating neurodermatitis. A few observers have noted the occurrence of interspersed small white areas which they have interpreted as a superficial type of atrophy, but true atrophy in the dermatologic sense (caused by advanced changes in the supporting tissues of the cutis) I have not yet encountered in dermatomyositis affecting this locality. When there are whitish, lentil to bean-sized areas of depigmentation scattered in the patches of pigmentation and when these are associated with enough edema to cause thinning of the epidermis, observers may regard such whitish areas as evidence of atrophy, without specifying precisely what they mean by this term.

Occasionally dilated follicles may be seen in the skin of the lids, and there may be fine white scales, often of the adherent type, which may be regarded as "eczematous." Livonius [3] observed delicate round and linear, porcelain-colored scars at the angles of the eyelids in an instance of this disease. Finally, these parts may show only telangiectasia in more or less compact patches, but at the most this finding of itself is a directing rather than a diagnostic sign.

The lesions in the eyelids are often not only the earliest cutaneous sign but frequently one of the initial manifestations in dermatomyositis. These alterations are usually more conspicuous than the other lesions on the face, and this disproportionate involvement is one of the striking features in the disease. As an early sign it is more likely to be seen in dermatomyositis than in systemic lupus erythematosus, but occasional apparent exceptions may be encountered, especially when the patient is seen late in the course. As a rule, however, implication of the eyelids in systemic lupus erythematosus is met with as a secondary spread from the main eruption on the "butterfly" area of the face in instances showing especially intense lesions in the flush regions, notably after exposure to sun. In advanced stages the differentiation may be more difficult, and in such circumstances the remainder of the clinical picture (cutaneous and internal medical) must be taken into consideration.

(*b*) *Remainder of the Face.* Facial lesions are commonly observed in dermatomyositis, although less often than involvement of the eyelids. Their chief importance lies in their similarity in many instances to the eruption in systemic lupus erythematosus.

In most cases there are faint delicate rosy plaques on the cheeks near the eyelids and the adjacent areas of the nose, and as in the case of the eyelids, numerous closely set telangiectatic areas are the principal component. In other patients the flush area of the face is affected in a manner resembling closely that seen in systemic lupus erythematosus. Thus, there may be observed a bright erythematous eruption arranged in "butterfly" configuration on the cheeks, whereas the bridge of the nose is often, though not always, spared. When there is a pronounced edematous element, erysipelas is simulated owing to the smooth, more or less tense and shiny appearance of the skin (the so-called pseudo-erysipelas or chronic erysipelas of some authors), but this appearance is likely to be encountered far more often in systemic lupus ery-

thematosus (figure 1). It must be stressed that the occurrence of an erythematous facial eruption in "butterfly" arrangement, even when accompanied by adherent scaling, is by no means pathognomonic of lupus erythematosus. For example, I have described such an appearance in a case of parapsoriasis en plaques disseminées terminating in mycosis fungoides.[4] Closely set telangiectasia is more frequently found in dermatomyositis, but, as a differential point from systemic lupus erythematosus, this feature must not be overstressed, as there are exceptions. As in the latter affection, scaling when present is likely to be adherent in type. This may be seen in any part of the face, especially the dorsum of the nose. In the acute phases of the eruptions seen in both diseases, follicular hyperkeratosis with prominence of the follicles is often lacking in the flush area of the face. These lesions may be observed more frequently in other areas, especially the forehead in dermatomyositis.

Generally the facial eruption in dermatomyositis remains visible for some time, even months or years, with occasional and unpredictable exacerbations in intensity. It may become fainter and show a delicate violaceous hue or a heliotrope color, and in the later stages it may be succeeded, though not invariably, by pigmentation. The pigmentation may be colored a light or dark brown, may be faint or conspicuous, and may occur as smooth or irregular patches or in a reticulated pattern with an admixture of contrasting small whitish areas, pinhead to lentil in size. The latter lesions have been interpreted by some observers as evidence of superficial atrophy but, as stated previously, the precise meaning of the term atrophy is not generally defined. The pigmented lesions may remain visible for months or even years, as in a case recently reported by me.[1a] This is the type of eruption that is often diagnosed as poikilodermatomyositis, especially when the pigmentation takes on a variegated pattern with an admixture of telangiectases in cases featured by an insidious development of muscular atrophy.

It appears, then, that the occasional example of dermatomyositis showing pronounced involvement of the flush area of the face can be differentiated with difficulty, if at all, from systemic lupus erythematosus on the basis of the facial lesions alone. In the acute phases of both diseases genuine atrophy in its restricted sense is generally lacking, and what is occasionally described as atrophy usually turns out to be simple thinning of the epidermis. For this reason complete regression of such lesions may occur, without leaving gross residual changes. So far as dermatomyositis and the majority of cases of systemic lupus erythematosus are concerned, atrophic discoid patches on the face are relatively uncommon. Pinhead to lentil-sized areas of so-called atrophy may be found sometimes in dermatomyositis. Where the atrophic patches on the face are larger (coin-sized, discoid), one is likely to be concerned either with the relatively less common type of systemic lupus erythematosus superimposed on the chronic discoid form of the disease [5] or the still more uncommon instances of disseminated atrophic lupus erythematosus accompanied by systemic manifestations. An instance of the latter syndrome has been reported by me.[6]

FIG. 1 (*Left*). The typical "butterfly" eruption of systemic lupus erythematosus (black arrows); the white arrow points to a swollen gland in the neck, a not uncommon finding in this disease and independent of tuberculosis.

FIG. 2 (*Right*). The dermatomyositic facies, more pronounced than usual, as exemplified in a case of Fuhs. The arrow points to the swollen, erythematous and telangiectatic skin of the eyelids. In the stage of pigmentation the term "poikilodermatomyositis" is generally used by dermatologists (see text).

The forehead and temples are commonly affected in dermatomyositis, and also in systemic lupus erythematosus, although less often. In some cases this region may be the initial site of involvement of the skin in dermatomyositis, and symmetrical pigmented patches are frequently the end-stage of lesions starting primarily as telangiectatic erythematous areas. The occurrence of small patches in the skin directly cephalad to the eyebrows, without pronounced involvement of the eyelids, is encountered more often in systemic lupus erythematosus than in dermatomyositis, but the reverse seems true in the case of patches on the forehead and temples, associated with follicular elevations. On the basis of these points alone it would be hazardous, however, to establish a differential diagnosis.

In dermatomyositis similar telangiectatic erythematous areas may also be seen occasionally on the upper lips, the chin and about the mouth. In some instances a perioral pallor is present, and this cannot always be correlated with the degree of secondary anemia.

No detailed description of the evolution of the lesions on the face has been given, for it is essentially the same as in the case of the eyelids.

The Dermatomyositic Facies

This is composed of two elements: (1) definitely swollen eyelids with narrowing of either one or both lid spaces together with a degree of edematous involvement of the adjacent portions of the cheeks and nose; (2) a background of faint rosy or pale blue colored skin (by some described as wine-colored). The net effect of these appearances is to create a sort of heliotropic bloating of the face, resembling the early stages of cadaveric decomposition. This type of facies is often seen and is easily recognized (figure 2).

In some instances it may be modified or obscured by accessory phenomena occurring in the subcutaneous and muscular tissues of the face.

(*c*) *Scalp.* Alopecia, total or incomplete, may occur in dermatomyositis. Often this seems to be related to the severity of the illness, especially the height of the fever, but this is variable, and there is nothing specific in this phenomenon. Causade and Aleshkowska [7] observed a cyanosed appearance of the skin of the scalp in association with total alopecia of this part. The hair may regrow with subsidence of the illness.

Commonly there occurs more or less diffuse redness or a violaceous erythema of the skin of the scalp, with telangiectasia, more or less scaling of a branny type, and preservation of the hair. Although these lesions may suggest the possibility of dermatomyositis, they are not distinctive, for similar manifestations may be seen in other diseases, including systemic lupus erythematosus. However, in cases of discoid lupus erythematosus with superimposed systemic lupus erythematosus, it is not rare to encounter genuine coin-sized atrophic patches in the scalp, and their occurrence, which I have observed in at least half a dozen instances, favors definitely the diagnosis of

lupus erythematosus. Such patches of coin-sized discoid atrophy I have not yet seen in any authentic example of dermatomyositis.

(*d*) *Ears.* In dermatomyositis the ears, especially along the rims, are often sites of erythematous areas generally the size of a pea or larger, and sometimes there is coalescence with formation of extensive patches. Here, too, telangiectasia is an important component of the lesions. Thickening and swelling of the lobes of the ears may be observed sometimes. It is not uncommon to find small areas of telangiectasia distributed irregularly along the rims. The erythematous lesions are frequently covered by adherent scales. Dilated follicular openings [8] and pigmented spots may be seen occasionally. Of greater interest is the occurrence of atrophic areas that often appear to be indistinguishable from those in systemic lupus erythematosus, except that as a rule these lesions are smaller and more discrete in dermatomyositis. Only in uncommon instances is there extensive atrophy of the ears, and rarely this may be of a character to permit the subjacent veins to shine through. Rare, also, is the occurrence of subcutaneous hemorrhages in these parts.[9] In occasional instances the area of skin behind the ears or in the retromandibular regions may be the earliest sites of eruption, with spread to contiguous or remote parts of the body. Exceptionally, small ulcerations may be found in the external auditory canal, which may be painful and recurrent.[10]

It appears, then, that the differentiation of dermatomyositis from systemic lupus erythematosus on the basis of these appearances is difficult, if not impossible.

(*e*) *Neck, Chest and Abdomen.* These parts are often implicated in dermatomyositis. The cutaneous changes are of two types which may occur independently or combined, and there are also transitions. These appearances may be modified, especially by edematous infiltrations involving the skin, subcutaneous tissues and muscles.

1. There are smaller and larger patches, discrete or coalescent, showing attributes similar to those already described: in the early stages, erythema of varying grades, telangiectasia and some scaling, usually of the fine adherent type; in the later stages, pigmentation in solid or reticulated pattern, with telangiectasia and interspersed whitish areas of irregular size and distribution, creating an appearance for which the term poikilodermatomyositis is often used. Occasionally the follicles may be seen as flat, raised, tiny, firm whitish or brownish elevations. With more pronounced edema, the affected areas are often tense, smooth, shiny and atrophic in the sense of a thin epidermis.

The V-shaped area of the neck is frequently involved in dermatomyositis, generally in the form of irregular pale red or faintly violaceous patches showing indefinite margins. In some of these cases, at least, the influence of exposure to sun seems manifest. This part of the body is affected more frequently in systemic lupus erythematosus in which its occurrence is the rule (figure 3). In systemic lupus erythematosus the outline of this lesion is often fairly circumscribed and more apt to conform to the portion of the neck left free by the dress (women) and to the exposed portion of the

bathing-suit, whereas the areas covered by the shoulder straps are generally spared. Instances exhibiting lesions with indefinite margins that fade gradually into normal skin are, however, also encountered in systemic lupus erythematosus, but this is the rule in dermatomyositis. In some cases of systemic lupus erythematosus the V-shaped area of the neck is the site of an

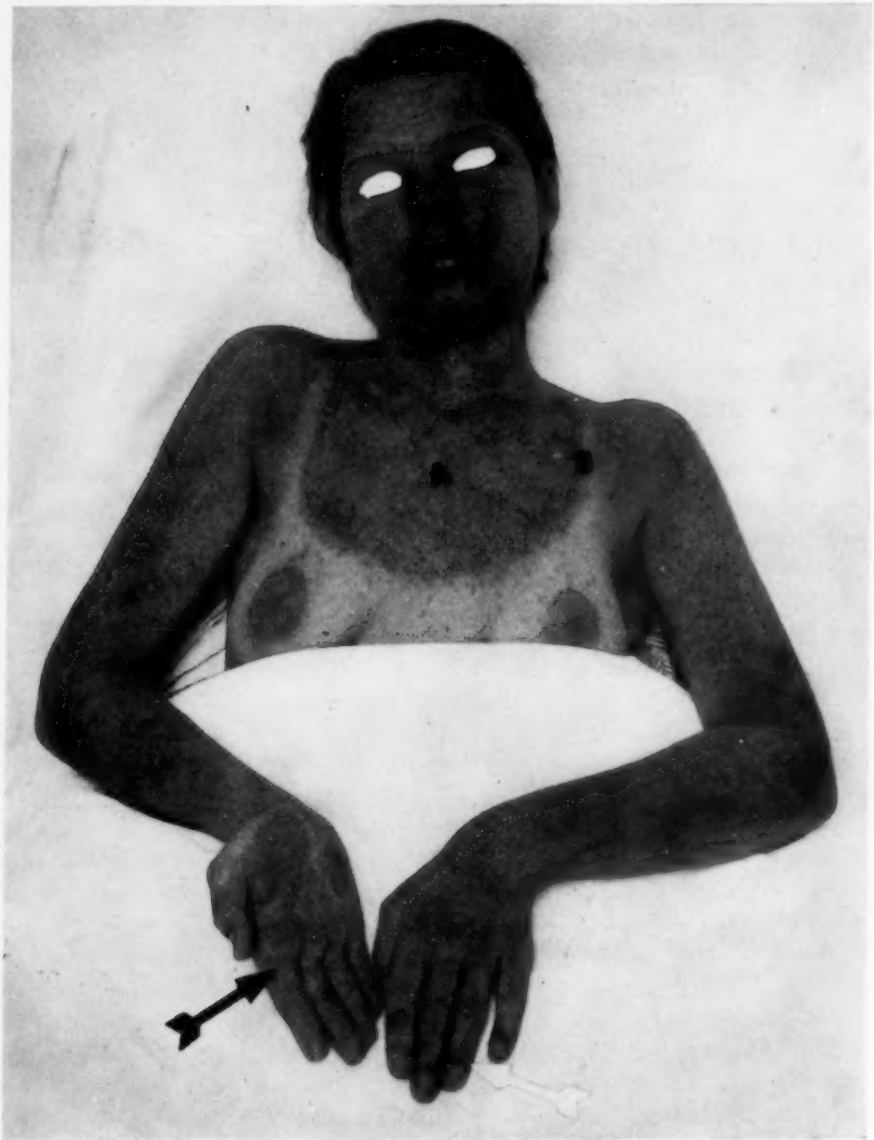

FIG. 3. Systemic lupus erythematosus in a young girl. Note involvement of the exposed portion of the chest (*A*) with sparing of the shoulder-strap areas (*B*). The black arrow points to the erythematous and telangiectatic lesions in the palms; the white arrow points to similar involvement of the skin about the nails.

eruption that progresses to form either a shiny, smooth, genuinely atrophic solid patch or many similar interspersed lesions. Such solid plaques of atrophy definitely favor the diagnosis of systemic lupus erythematosus as against dermatomyositis.

On the other hand, the posterior aspect of the neck is far more often involved in dermatomyositis. The occurrence of diffuse pigmented patches in the nuchal region with spread to the lateral portions of the neck is, perhaps, in some ways distinctive of dermatomyositis, and not rarely may be the initial site of the eruption. Cutaneous lesions behind the ears, in solitary and discrete areas, are seen in both systemic lupus erythematosus and dermatomyositis.

In some instances of dermatomyositis the resemblances to pellagra seem considerable because of the pigmentation of the neck (vaguely resembling Casal's collar), pigmentation of the face, alterations in the oral mucous membranes, patches on the dorsa of the hands (which are, however, vastly different in appearance), etc. On several occasions I have encountered instances in which the diagnosis of pellagra or of riboflavin deficiency or some such avitaminosis had been entertained, and it seems to me that the pendulum of vitamin B deficiency needs considerable steadying. Dermatomyositis, it may be noted, is also a disease in which exposure to sun often exerts an influence on the eruption and its localization.

The pigmentation in dermatomyositis may be so intense and widespread as to simulate Addison's disease. The finding of a low blood-sodium is not adequate to determine the differential diagnosis.

2. Less frequently there are encountered, chiefly on the anterior and posterior aspects of the chest, but also on the neck, abdomen and other parts, small areas of atrophy [11] similar to those to be described in connection with the skin overlying the articulations. These lesions, pinhead to a pea or larger, are often the clinical counterpart of what dermatologists call "white spot disease" or the "visiting card" type of scleroderma. However, the differentiation of the atrophic lesions in dermatomyositis from "white spot disease" (a heterogeneous group of cutaneous anomalies) is not difficult in view of the associated features in the skin and the distinctive systemic manifestations. These appearances in dermatomyositis are of interest in showing that this type of atrophy (involving the supporting tissues in the upper cutis as well as thinning of the epidermis) is not pathognomonic per se of a single disease but must be evaluated on the basis of the entire clinical picture. Such small areas of atrophy, occasionally grouped, are more often seen in dermatomyositis than in systemic lupus erythematosus, and their relatively common occurrence on covered portions of the body seems noteworthy.

The cutaneous alterations in dermatomyositis, especially those on the trunk, have been compared by some observers with radiodermatitis, but in reality the resemblances are superficial. In dermatomyositis the involved areas are as a rule larger, often covering extensive tracts of skin; the telangiectasia is finer, more closely set and more regularly arranged; the peculiar

sclerosis of true skin as found in radiodermatitis is absent, although it may be simulated in advanced stages of dermatomyositis, particularly when the underlying muscular and subcutaneous tissues have undergone atrophy; the painful ulcerations of radiodermatitis never occur, although occasionally in dermatomyositis there may be ulcerations arising from a variety of causes to be mentioned later; there is no history of the use of roentgen-ray, radium or ointments containing radioactive substances (if there is such a history, the lesions extend far beyond the point of application of these therapeutic agents); and, finally, the clinical picture as a whole, both cutaneous and systemic, is vastly different in these two affections.

f. The Limbs. (1) Eruption over the articulations: To discuss these lesions as a unit is not arbitrary, for in most cases of dermatomyositis the skin overlying the joints is affected characteristically, whereas the intervening portions of the limbs are spared. Indeed, a few observers have stressed this localization about these so-called pressure points. Study of this aspect of the eruption provides data substantiating the view that dermatomyositis pursues a variable course ranging from the mild cases to the acute, subacute and chronic forms with their transitions into the clinical pictures of myositis fibrosa, myositis ossificans, etc. These observations, moreover, shed more light on the concept of this disease and, especially, the prognosis.

For convenience this group of lesions may be discussed under the following two headings: (*A*) those related to the small joints, particularly of the fingers; (*B*) those related to the larger articulations.

(*A*) The lesions found in the skin overlying the small joints of the hands in dermatomyositis represent an outstanding feature of this disease in all its stages. In many cases they appear as the initial manifestations. By themselves these alterations are highly characteristic and take on the attributes of a pathognomonic appearance, notably when correlated with the remainder of the clinical picture. In obscure cases these lesions may constitute a "revealing" sign. Without in any way detracting from the importance assigned to them by Gottron,[11a] it will be seen later that other diseases are accompanied by somewhat similar manifestations, but, as a rule, their differentiation is not difficult.

In the early stages these lesions appear in the form of ill-defined, somewhat edematous, blotchy red telangiectatic patches situated over the metacarpo-phalangeal and interphalangeal joints. In some cases only a few of these articular regions are affected, but generally the eruption is bilateral and often symmetrical. The cutaneous lesions over the metacarpo-phalangeal joints are observed more often and in more characteristic form than those in relation to the interphalangeal joints, although both are frequently affected together. Sometimes, also, the plaques are fairly well outlined. In most instances the lesions are dull red, violaceous, or have a cyanosed hue, but as in the case of the eyelids, telangiectasia commonly forms the major component. It will be remembered that these localities are sites of terminal circulation, and the color of lesions often depends upon the state of the circulation in these

areas. The ectatic vessels, when less numerous, are easily overlooked, as, for example, in the case of Milian and Rimé [12] in which no mention was made of them until their presence was pointed out as a curious feature by Lortat-Jacob [13] in his discussion of that case. On a number of occasions I have also seen these lesions overlooked. Most often there is seen a fine adherent type of scaling, and undoubtedly it is this feature that has caused a few observers to speak of a dry dermatitis.[14] In occasional examples I have encountered gradually increasing pigmentation over the knuckles, without a preceding telangiectatic or erythematous eruption, so far as I could tell. Such pigmented patches, generally ill-defined in their contours, may be seen sometimes in other affections, such as ordinary rheumatoid arthritis, and cannot be regarded, therefore, as bearing special significance. Pick [15] described the occurrence of necrotic hemorrhagic areas in the skin overlying the phalangeal joints of one hand. Warszewski and Radzinski [16] recorded the presence of peculiar vesicular lesions over the metacarpo-phalangeal joints. Incisions of the vesicles yielded a small amount of thin, apparently nonpurulent fluid. The phenomena observed in these two cases represent examples of a more intense exudative process such as is rarely encountered in this situation in dermatomyositis, but such lesions are met with occasionally in this disease in other parts of the body, usually as isolated manifestations.

When circumscribed plaques are formed, they appear as bluish-red areas with a fringe of telangiectatic vessels, often associated with dilated capillaries that course over the central portions of the lesions. This appearance may be retained for weeks or months, may disappear, or may go on to assume any one of the following characteristic aspects:

a. The lesions may consist of a mosaic of papules in close apposition to one another, so that the normal lines of skin seem exaggerated (figure 4). There may or may not be a degree of atrophy, but, according to my clinical observations, this would be restricted to simple stretching of the epidermis. The pseudo-lichenification in these generally nonpruritic plaques has often been confounded with neurodermatitis, according to my observations, but on the other hand, the bluish color may remind the observer of lichen planus. This mosaic appearance is common and is often attended with more or less scaling of an adherent type.

b. The lesions may be sites of "soft" atrophy (figure 5) similar to that seen in acrodermatitis chronica atrophicans, occasionally epidermolysis bullosa dystrophica. Although this appearance may be best witnessed in the skin about the larger articulations, it is also encountered in characteristic form over the small joints. The skin is thin, wrinkled, shiny, slightly scaly and often colored bluish-red with a superimposed livid hue.

c. In other cases there are observed whitish plaques resembling porcelain or alabaster, with some depression of the central portions and a surrounding zone of telangiectasia. These vary in size from that of a pea to an area covering the entire knuckle, especially over the metacarpo-phalangeal joints.

Owing to the anatomical relations of the knuckles, these atropic lesions are apt to create the impression of pronounced infiltration, and, from their appearance and feel, may be regarded as an example of "hard" atrophy. This effect is enhanced by the hyperkeratosis (scaling) commonly encountered in these areas. In some instances these changes are so pronounced that the lesions seem to be adherent to the underlying bone, without in any way resembling scleroderma.

(*B*) Similar changes may be found in the skin about the larger joints, such as the elbows (figure 6), knees, ankles, wrists, etc. In my observations the elbows were the most frequent sites and were nearly always associated with involvement of the knuckle areas. Dowling [17] recorded an instance in which the initial manifestations appeared about the elbows, only to disappear later. Most commonly there are observed reddish-blue or dull red flat patches showing a striking telangiectatic element and adherent scales. When scaling is pronounced, psoriasis may be simulated vaguely, as, for example, in Semon's case.[18] In later stages the skin takes on attributes resembling those seen in acrodermatitis chronica atrophicans or healed epidermolysis bullosa dystrophica, and becomes thinned out, wrinkled, and like cigarette-paper. According to my own observations, this "soft" type of atrophy is especially common. I have not yet had the opportunity of seeing the alabaster-like, whitish, "hard" atrophic patches in areas of skin about the larger articulations, such as is seen so often over the knuckles. However, Schuermann [11b] observed porcelain-like spots over the malleoli and patellas. Bamber [19] saw whitish depigmented macules over the wrist, associated with telangiectasia, but he was not certain that these spots were actually atrophic. I have seen the skin over the knees discolored a deep reddish-blue, such as may be commonly found in patients with chronic cardiac failure, and once I encountered a telangiectatic eruption about the ankles, the telangiectases being arranged in circular formations with simulation of Majocchi's disease (purpura annularis telangiectodes). The knees may be sites of pigmented patches with a surrounding zone of telangiectasia.[19]

Since much clinical significance has been assigned to the eruption about the articular areas, especially the small joints of the hands, it seems desirable to discuss, according to my own observations, some of the many diseases that may be accompanied by similar manifestations.

a. Systemic Lupus Erythematosus. In this affection the cutaneous areas about the articulations are sometimes affected, but on a comparative basis such changes are encountered far more often in dermatomyositis. A few instances of systemic lupus erythematosus with knuckle lesions have been

FIG. 4 (*Above*). A case of dermatomyositis in a child. The "mosaic" lesions on the knuckles (*A* and *B*); erythematous and telangiectatic skin about the nails with involvement of the proximal nail folds (*C*).

FIG. 5 (*Below*). A case of dermatomyositis in a young man. The "atrophic" lesions on the knuckles (*A* and *B*); atrophy of the interosseous muscles illustrated at *C*. Compare the knuckle lesions with those seen on the elbows of the same patient (figure 6). (From Keil, H.: Arch. Int. Med., 1940, lxvi, 109.)

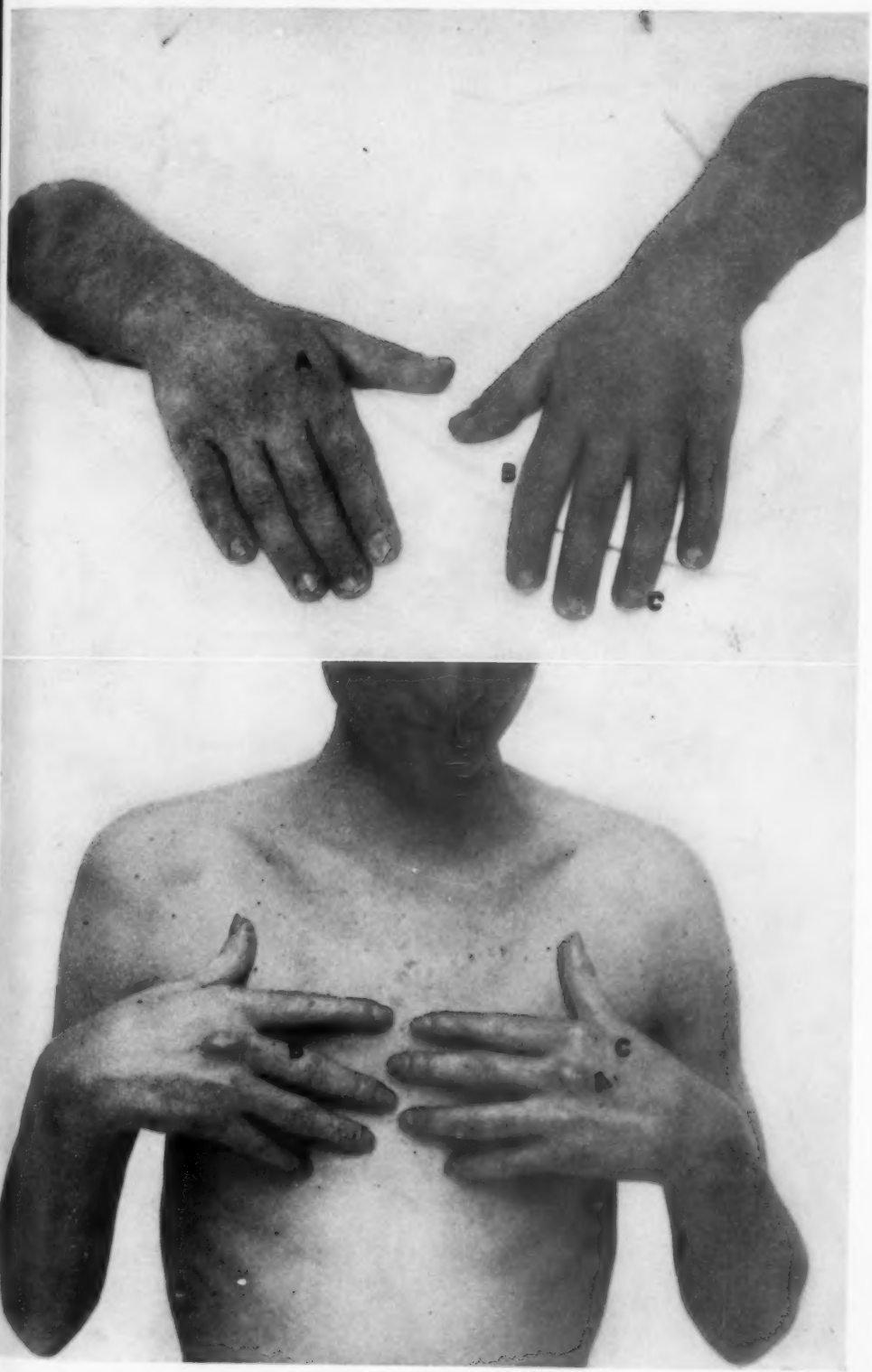

FIG. 4 and FIG. 5.

recorded, but where adequate clinical details are available, as in Klingmüller's case, it appears that the condition was in reality dermatomyositis. It must be admitted, however, that the differentiation in such instances may be difficult at times, if not impossible at certain stages. I have encountered at least

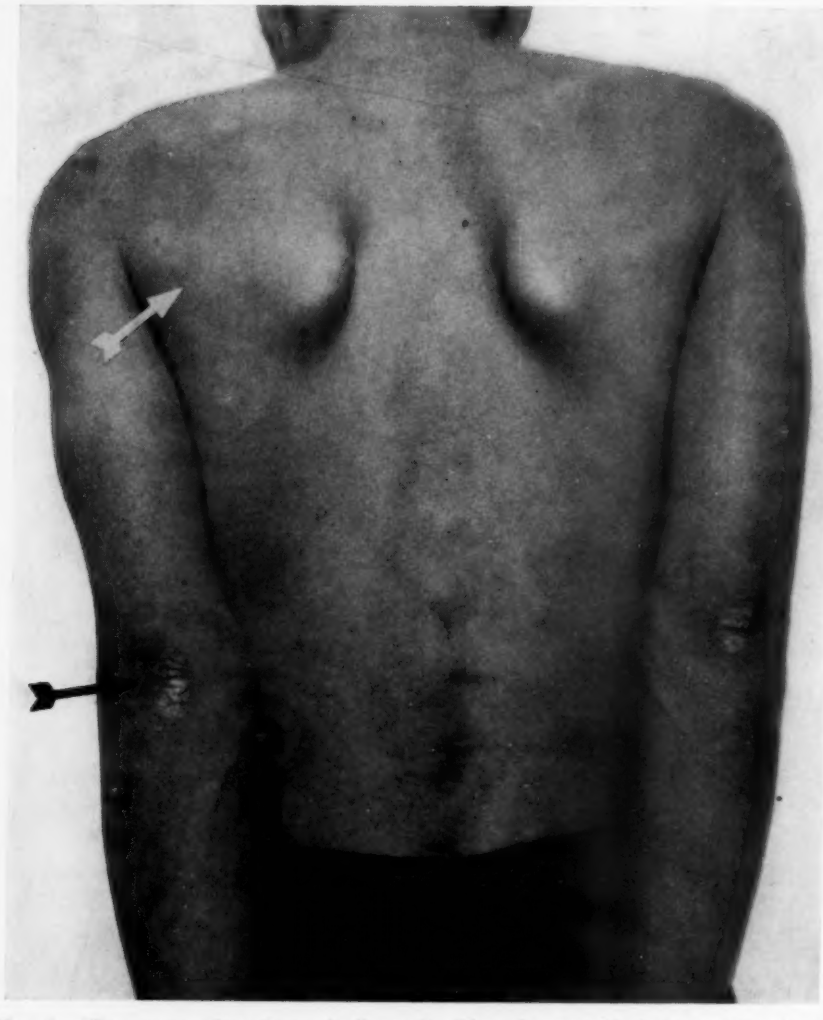

FIG. 6. The same patient shown in figure 5. Note the atrophic lesions about the elbows and their striking resemblance to acrodermatitis chronica atrophicans and to the healed stages of dystrophic epidermolysis bullosa. The white arrow points to the general area showing atrophy of the shoulder-girdle muscles and the arms. (From Keil, H.: Arch. Int. Med., 1940, lxvi, 109.)

three patients in whom whitish depressed atrophic patches with peripheral bright red rims of erythema and telangiectasia occurred irregularly over the dorsa of the fingers, but it is interesting to note that these lesions were distributed at random between the small joints. Although, therefore, the

knuckle lesions in dermatomyositis are not pathognomonic per se, their occurrence provides, at the very least, a significant "revealing" sign, and their importance becomes enhanced when they are evaluated in terms of the other features in this disease. In some instances, and these are becoming fewer in number, the differential diagnosis between dermatomyositis and systemic lupus erythematosus will rest on the composite clinical picture and the subsequent course.[1]

b. Acrodermatitis Chronica Atrophicans. The lesions about the articulations in dermatomyositis, especially the larger joints, exhibit considerable resemblance to acrodermatitis chronica atrophicans (figure 6). This is particularly true of the early stages of the latter disease, when the eruptive elements are more or less confined to the immediate neighborhood of the large joints, such as the elbows. However, in the later stages a number of differences are found: (1) in acrodermatitis chronica atrophicans the skin becomes so thin as to permit the subjacent veins to shine through, but such a degree of atrophy is uncommon in dermatomyositis; (2) in acrodermatitis chronica atrophicans there is spread to involve large tracts of skin with the "soft" type of atrophy characteristic of this disease, but such extension of atrophy of this type I have not encountered in dermatomyositis, nor do I know of its occurrence in any recorded case; (3) in acrodermatitis chronica atrophicans it is common to encounter linear sclerotic-like bands along the ulnar bones, etc., which seem not to occur in dermatomyositis; (4) the systemic features and the other clinical manifestations are vastly different in these diseases.

c. Epidermolysis Bullosa Dystrophica. In the healing or healed stage of epidermolysis bullosa dystrophica the skin about the knuckles and the larger joints may be sites of lesions that are the counterpart of the cigarette-paper-like atrophic patches in dermatomyositis. The former affection is distinguished by the frequent onset at birth or shortly after, the familial history, the commencement with bullae, the frequent concomitance with dystrophic changes in the nails, the oral manifestations that are often frankly bullous, rarely the conjunctival alterations in the nature of "essential shrinkage," etc. The general symptoms of dermatomyositis, including the muscular phenomena and the other cutaneous changes, especially in the face, are absent in epidermolysis bullosa.

d. Chronic Cardiac Failure. In chronic cardiac failure, particularly that associated with rheumatic heart disease, involvement of the skin overlying the knuckles, elbows, knees, etc., occurs sometimes. These lesions appear as superficial patches colored reddish, reddish-blue or purple red (local cyanosis), accompanied occasionally by hyperkeratosis (scaling) of variable degree. The latter may attain an enormous degree of development in some instances.[20] Generally these areas are colder to the touch than the neighboring parts, and it must be stressed again that they represent points of terminal circulation. These lesions are probably analogous to the so-called "mitral flush or facies" observed in long-standing examples of mitral stenosis, and to chronic passive

congestion of the viscera seen in postmortem examinations in such instances. Commonly there are associated follicular-papular lesions on the legs and forearms, similar to those seen in chilblains and in women with "poor circulation." In addition, it is relatively common to find reddish brown papules, often with scratched tops, sometimes more or less grouped (usually less) about the articulations, and generally healing with the formation of centrally depressed scars enclosed by a peripheral narrow ring of pigmentation. In the healing or healed stages papulonecrotic tuberculides are simulated, but in my view these manifestations have an entirely different significance from the somewhat clinically similar tuberculides found especially in children suffering from active lymph node tuberculosis with generalization of the infection (secondary stage of Ranke).

The lesions about the articulations may, therefore, more or less resemble those in dermatomyositis, but in chronic cardiac failure they represent part of an entirely different clinical picture.

e. Rheumatic Subcutaneous Nodules. In occasional instances, of which I have seen one striking example, the presence of rheumatic subcutaneous nodules in the tendons passing over the metacarpo-phalangeal joints may cause redness of the overlying skin. Generally only a few knuckles are affected irregularly. This appearance is probably caused by local pressure on the superficial skin over the joints, for, as the subcutaneous nodules diminish in size, the redness disappears. Scaling seems not to occur. At least it was not present in the case under my observation.[21]

f. Angiokeratoma of Mibelli. This condition affects the skin over the bony protuberances of the limbs, especially the hands and feet, sometimes the knees and elbows. When situated over the knuckles, the lesions may simulate closely those found in dermatomyositis. As a rule the eruption is composed of discrete, isolated, rough, hard and warty bluish papules, pinpoint to pinhead in size. Diascopic examination shows dark red puncta corresponding to enormously dilated capillaries or actual hemorrhagic extravasation, and pricking with a needle is likely to lead to free bleeding. In addition to the above localizations, the lesions are often scattered irregularly over the fingers, toes and dorsa of the feet. This affection occurs in young adults of both sexes, generally has its onset at an early age in persons, especially girls, with a previous history of chilblains or pernio, and is occasionally seen in association with lupus erythematosus. The morphology of these lesions as well as the general clinical picture distinguish this disease from dermatomyositis.

g. Kaposi's Idiopathic Hemorrhagic Sarcomatosis. In some instances of this disease the eruption shows a definite predilection for the skin situated over the small joints of the hands as well as the large articulations. In the average case this affection is easily differentiated by the occurrence of peculiar reddish brown or reddish blue plaques near the terminal parts of the digits, the presence of nodules, the fairly distinctive color of the lesions, the characteristic changes in the lower limbs with the keratotic areas over the toes and the frequently associated "elephantiasis" of the legs, the special tendency to

the supervention of sarcomatous changes, the entirely different clinical course with involvement of lymph nodes, spleen, gastrointestinal tract, etc. It must be stressed that (*a*) this disease may also occur in children in whom it is perhaps a little more difficult to recognize; (*b*) a part of the cases originally classified as erythema elevatum diutinum (q.v.) represented in reality examples of Kaposi's hemorrhagic sarcomatosis.

h. Erythema Elevatum Diutinum. In typical cases of this affection there are observed bluish red, circumscribed, flat, button-like, infiltrated, more or less persistent plaques situated over the joints, especially the small articulations of the hands and larger joints, such as the elbows, knees and ankles. In their further evolution these lesions disappear, often leaving pigmented spots as sequelae.

Study of cases formerly included in this category indicates the heterogeneity of the group.[21] Thus, examples of subcutaneous nodules in rheumatoid arthritis, Kaposi's sarcomatosis, granuloma annulare and probably other affections have been included in older reports. Weidman and Besancon [22] made an outstanding effort to establish this entity on clinicopathologic grounds, but in my view the nosologic status of this disease is still far from clear. Above all, it cannot be accepted that this eruption, assuming that the two cases described by Weidman and Besancon were of the same nature, represents a "rheumatic" dermatosis, unless one wishes to employ this name in a vague sense. It is interesting that rheumatic fever is one of the common diagnoses for cases that eventually turn out to be dermatomyositis. I have recorded [1a] two such instances, and a critical review of other similar cases indicates clearly that the initial impression of rheumatic fever could not be substantiated post mortem. Weidman and Besancon described certain anatomical findings as characteristic, perhaps pathognomonic, of erythema elevatum diutinum, but complete acceptance of this view awaits study of a larger casuistic material. The illustration of the eruption on the hands in their second patient [23] is a replica of what I have described in dermatomyositis; figure 4 in this article may be compared with their figure 10.

Once I encountered an unusual instance showing similarities to erythema elevatum diutinum. Early in the course there were resemblances to erythema multiforme exsudativum and lupus erythematosus owing to the presence of lesions over the small joints of the hands, the ears and face. This was probably an example of extracellular cholesterosis. In a case recently reported by Gately and Ketron [24] as one of erythema elevatum diutinum, it is interesting that Urbach mentioned the possibility of extracellular cholesterosis in the discussion of this case. The resemblance between these two diseases is enhanced further by the occurrence of joint pains in both, or at least pains that have been interpreted as being of articular origin.[25]

i. Miscellaneous Affections. Many other conditions are sometimes accompanied by alterations in relation to the knuckles; for example, xanthoma tuberosum multiplex, xanthoma diabeticorum, gout, psoriasis, neuroder-

matitis, certain congenital anomalies, Raynaud's disease, scleroderma, etc. It is not difficult, as a rule, to differentiate the various manifestations of the aforementioned diseases from the appearances in dermatomyositis.

2. *Remainder of Limbs.* (*a*) Proximal portions (arms, forearms, thighs and legs). The areas of limb between the joints are generally spared, with certain exceptions to be mentioned later in discussing the skin-muscle relationship. The continuity of skin over the limbs is more apt to become involved when the exanthem takes on a widespread distribution, and in such cases the extensor aspects of the limbs are usually favored. However, the flexor aspects (flexures of elbows and knees, etc.) may show edema and fissuring. In Towle's case [26] the skin became so tense that it broke at the bend of the elbow and the inner aspect of both thighs, resulting in hernial protrusions of the subcutaneous fat [27] but such a phenomenon belongs to the rarities. The eruption on the limbs is the counterpart of the lesions previously described. In instances featured by a universal distribution and pronounced scaling, the picture of an exfoliative dermatitis may be produced.[28]

(*b*) Distal portions (hands and feet). Under this heading a few interesting manifestations remain to be mentioned, among them certain "vasomotor" phenomena.

1. In addition to the characteristic knuckle lesions, there are commonly associated with them telangiectatic and scaling small areas colored red to reddish blue and situated between the distal interphalangeal joints and the proximal nail folds, with encroachment on the latter structures (figure 4). These appearances are often duplicated in systemic lupus erythematosus (figure 3) and probably other diseases, hence they are distinctive in only a limited degree. I have seen cases labeled as systemic lupus erythematosus on the basis of these lesions in obvious examples of dermatomyositis.

In a number of recorded cases the eruption on the hands has been diagnosed originally as occupational dermatitis, so that this disease sometimes has medicolegal implications. I have recorded two such examples and reviewed the factor of lead in its possible relation to the onset and accentuation of dermatomyositis.[1] Hendry and Anderson [29] reported the case of a photographer's assistant in whom a positive patch test to hydroquinone was obtained, but the significance of this finding was impaired because of the patient's improvement despite continuation at work.

2. The fingers and toes, especially the former, are often sites of phenomena generally classed as vasomotor in origin. These include paresthesias (numbness, tingling, etc.) and acrocyanosis of various grades with transitions into a clinical picture resembling Raynaud's disease. In a group of 40 cases of dermatomyositis O'Leary and Waisman [30] recorded the occurrence of paresthesias in nine patients and acrocyanosis or variants of this state in 10 instances. They noted that the paresthesias were neither pronounced nor constant. The same seems to be true of the phenomena classed as acrocyanosis, and in order to stress their relative mildness in these cases the term

pseudo-Raynaud's syndrome is used. As a rule, the attacks, which may appear either as an initial manifestation or as an intercurrent event, are limited to the first stage of local syncope (fingers white and "dead"), occasionally the second stage of asphyxia (blue fingers), but rarely the final phase of gangrene. These attacks occur generally in the winter. In Ingram and Stewart's patient mild episodes of acroasphyxia appeared during each of the three winters preceding the onset of dermatomyositis.[31] Bailey [32] reported an instance in which there was a previous history of chilblains at an early age. I [1a] described the case of a young man who had several such attacks intercurrently, and it may be noted that a relatively high percentage of such patients were men.

In another publication [1b] the point has been stressed that a pseudo-Raynaud picture may be encountered in a number of affections, such as dermatomyositis, systemic lupus erythematosus, scleroderma, etc. Some observers have attempted to ally these diseases on the basis of these vasomotor manifestations, but this view is hazardous. Whether similarity in pathogenesis necessarily means identity in etiology seems doubtful, and this fundamental problem still remains to be clarified.

From time to time observers have also attempted to establish an absolute relation between scleroderma and dermatomyositis. This hypothesis, based chiefly on analogy, may be regarded as lacking in proof. On this point my views are in complete accord with those set forth recently by O'Leary and Waisman [30] who also sharply differentiate these diseases.

3. There came under my observation a probable example of systemic lupus erythematosus, the only one I have seen with undoubted involvement of the large muscular groups, in which the ventral surfaces of the distal ends of all the fingers were sites of a deep red, sharply circumscribed eruption. These lesions occupied about an inch of the surface and extended toward the free margins of the nails on the dorsal aspects. The appearance simulated somewhat that seen in psoriasis. This case is mentioned as a curiosity in view of the definite muscular involvement in a case in which the findings at necropsy were consistent with the diagnosis of systemic lupus erythematosus. However, as I saw the patient on but one occasion and had no real opportunity to study the clinical course, it seems wise to suspend judgment until more examples of this type are observed.

Schatzki [33] described an instance of dermatomyositis in which the large toes were sites of a few scattered erythematous painless lesions. Such spots are not to be confounded with the Osler nodes.[21]

4. Palms and Soles. Involvement of the palms and soles is uncommon in dermatomyositis. In this respect there is a definite contrast between this disease and systemic lupus erythematosus, for in the latter affection these areas, especially the palms, are frequent sites of red or reddish blue, discrete and coalescent spots (figures 3 and 7). A few observers have recorded examples of dermatomyositis that are exceptions to the above rule. Thus, Crevald [34] saw large red spots on various parts of the palms. Pick [15] de-

scribed a case in which he observed, in the terminal stage, lentil-sized, bluish-violet, non-circumscribed painless spots in the palms. Such lesions may more or less resemble Janeway spots,[21] and it may be noted that in this case the postmortem examination revealed no evidence of acute bacterial endocarditis. Dohi [35] recorded the occurrence of many telangiectases in the palms and soles, with the epidermis being apparently thinner than normal. In one of my cases there had been a punctate type of keratoderma.[1a] Wolf and Wilens (case 1)[36] described an example of dermatomyositis in which the onset occurred with a "dermatitis" of the palms. These are all exceptional observations. Involvement of the palms and soles, especially the former, speaks definitely for systemic lupus erythematosus as against dermatomyositis.

Petges and Petges,[2] discussing poikilodermatomyositis, also stressed the rarity of such lesions in this disease. In my view [1b] this syndrome is merely a morphologic variant of ordinary dermatomyositis.

5. Nails. Involvement of the structures about the nails is but rarely mentioned in accounts of dermatomyositis, yet such changes are often seen (figures 5 and 8). The occurrence of erythematous and telangiectatic lesions in the soft parts about the nails is fairly common, and, as a rule, they may be found along the rims of both the proximal and lateral nail folds. As stated, similar changes are encountered in systemic lupus erythematosus and probably other diseases. Of greater diagnostic significance is the appearance of hyperkeratotic alterations involving chiefly the proximal nail fold, occasionally portions of the lateral nail folds. These are recognized as yellowish tissue that projects irregularly or unevenly for a short distance over the lunula. Sometimes the changes are slight, but within the past few months I have seen three instances exhibiting these lesions in pronounced form. All of these cases were associated with alterations in the skin about the knuckles and the soft parts immediately surrounding the nail folds. In one instance there were also subungual hyperkeratotic accumulations underneath the lateral margins of the thumb nails, but such changes are much less important. It is my belief that hyperkeratosis involving the proximal nail folds is analogous to the whitish leukoplakia-like patches found in the oral mucous membranes (q.v.). It appears that anatomical peculiarities may explain the yellowish color of the former and the whitish appearance of the latter. Occasionally similar lesions are seen in the toes (figure 8). In some instances [11b, 15] these alterations are covered partly by crusted areas which on removal reveal superficial defects. The changes in the nail folds may undergo complete involution.

On the other hand, the nail plates are practically always spared. At least the changes are neither pronounced nor distinctive. Ingram and Stewart recorded an apparent exception, a patient who had dystrophic nails. The description of the changes (brittle nails) indicates that there was no comparison with the severity of the alterations observed, for example, in dystrophic epidermolysis bullosa. Moreover, it seems possible that in their case there was some relation to the Raynaud-like attacks in the fingers. I have

FIG. 7 (*Left*). A case of systemic lupus erythematosus in a child. The erythematous, telangiectatic and slightly hemorrhagic lesions in the palms and ventral aspects of the fingers (*A* and *B*).

FIG. 8 (*Right*). From the same patient as in figure 4 (after Engelhardt). To illustrate the lesion in the proximal nail fold of the large toe.

not seen massive hemorrhage into the nail beds as may occasionally occur in systemic lupus erythematosus.[6]

The incidence of the hyperkeratotic lesions about the proximal nail-folds is probably fairly high. These changes are often overlooked because they are not conspicuous. Occasionally they may appear as one of the early signs of dermatomyositis.[37] It is difficult to state at present whether these manifestations are distinctive. Although I have, thus far, not met with them in systemic lupus erythematosus, a recent case of diffuse progressive scleroderma under my observation showed similar lesions.

g. Miscellaneous Areas of Skin. The buttocks and sacral regions are occasionally affected, rarely the scrotum. The evolution of the lesions is analogous to that already described, and in these situations the eruptions lack specific attributes. Involvement of the buttocks by telangiectatic and superficially atrophic patches may only vaguely simulate the characteristic changes in acrodermatitis chronica atrophicans.

Mucous Membranes

The term dermatomucomyositis, first introduced by Oppenheim to designate the oral manifestations, is now considered superfluous, as these appearances are an integral part of the disease. Schuermann [11b] collected the records of more than 50 cases showing these lesions, an incidence of about 20 per cent. This is a conservative estimate, for owing to a number of technical difficulties, the mucous membranes are usually studied with less care. Of these parts the mouth and pharynx are most frequently affected, the larynx, conjunctiva and nose less commonly. Schuermann and his pupil, Memmert [38] have reviewed the subject exhaustively. In the main my observations are in close accord with theirs, although in the account to follow certain differences in the evaluation of the lesions will be discussed.

Before considering the subject, several points need to be mentioned: (*a*) the morphology of lesions in the mucous membranes is influenced considerably by a variety of anatomical factors [39]; (*b*) in some diseases there is an inherent tendency toward polymorphism in the enanthem, whereas in other cases this multiformity in appearance is due, in large part, to superimposition of such secondary phenomena as maceration of sputum, etc.; (*c*) although in dermatomyositis various lesions may be observed in the mucous membranes, only an occasional type can be considered as being somewhat distinctive. The remaining appearances are, therefore, best remembered in a negative way. In general, the lesions in the mouth and other parts resemble closely those seen in systemic lupus erythematosus, leukoplakia, lichen planus, occasionally syphilis, etc.

A. Mucous Membrane of the Mouth and Upper Respiratory Tract: 1. *Erythema.* This occurs as pinhead to lentil size or larger, flat, bright red areas involving any portion of the oral mucous membrane, and less commonly, isolated parts of the larynx and rarely the nose. In some instances

there is diffuse involvement of the mouth, and the process may extend down the pharynx and occasionally also the larynx. In many cases telangiectases, isolated or more compactly arranged, are found, but such appearances are hardly distinctive.

Instead of being colored a bright red, the lesions often assume a dusky red or bluish red color, and careful examination of such areas reveals frequently the presence of closely set telangiectatic vessels. In other cases there is superimposed an edematous element. This feature has clinical importance when there is implication of such structures as the larynx, and it may be an occasional cause of hoarseness, etc. In the mouth proper this bluish-red, edematous appearance is seen particularly in or near the margins of the gums, and such areas are prone to bleed readily. These lesions have been occasionally mistaken for scurvy or acute leukemia. In dermatomyositis there is no special predilection for the interdental papillae as is the case in scurvy. In a few instances the tongue may become more or less denuded of its epithelium, and such examples are occasionally regarded as pellagra.

The cases showing a widespread enanthem or severe subjective symptoms, such as profuse salivation, etc., are sometimes dignified by the title of stomatitis. The subjective complaints are best considered at the end of this section, for in many instances it is difficult to tell whether they are caused by changes in the mucous membranes proper or alterations in the deeper structures.

2. *Simple Edema Without an Erythematous Component.* Occasionally this type of edema involves such portions of the mouth as the tongue, gums, soft palate, floor of the mouth, etc., and this phenomenon seems to be the counterpart of what is observed in the skin and the underlying tissues. This manifestation has special importance when it occurs in the glottis or other parts of the larynx.[40] In rare instances operative intervention by tracheotomy may be essential for the relief of obstruction to breathing.[41] There may be mechanical difficulty in extruding the tongue which is swollen and painful, but this seems not to attain the degree of macroglossia observed, for example, in atypical amyloidosis, hemophilia, etc. The gums are occasionally swollen, and, when this is associated with bleeding, take on a spongy appearance simulating somewhat that seen in scurvy and acute leukemia.

3. *Hemorrhage.* The bluish-red appearance of lesions in the mucous membranes is caused, for the most part, by dilatation of the superficial capillaries, and, as such, this appearance is not classed under the head of true hemorrhage. Extravasations of blood into the tissues in the form of purpuric spots or larger deposits are uncommon. Oppenheim[10] recorded two cases in which "submucous suggilations" were observed in the cheeks, palate and posterior portion of the pharynx, with the subsequent formation of residual pigmented areas. In a few instances I have seen petechial spots, especially on the hard palate, and these lesions, which were generally few and isolated, may have represented traumatized and ruptured telangiectatic vessels. In any event, these petechiae possess no unusual clinical significance.

As noted previously, bleeding gums are sometimes encountered and in some cases small hemorrhages occur in other parts of the mucous membranes, including the nose. There is, however, no precise correlation between bleeding in the mucous membranes, the occurrence of purpura in the skin and the platelet count which is often but not always reduced. It is justifiable, therefore, to assume that local vascular damage, probably of a nonspecific type, is generally the important factor in the production of such hemorrhages.

4. *Vesicles.* In some instances vesicular lesions bordered by a greater or lesser erythematous halo are observed on the tongue, gums, palate and other areas of the mouth. These manifestations often simulate ordinary aphthous stomatitis or herpes of the oral cavity. In some cases they are forerunners of eroded or more deeply ulcerated areas. The lesions are best remembered in a negative way.

5. *Erosions and Ulcerations.* In dermatomyositis the mouth occasionally shows isolated or multiple, superficially eroded lesions occurring chiefly on the hard and soft palates, lips and tonsils; less commonly, on the nose and larynx. As in systemic lupus erythematosus, the borders are often colored a bright red to bluish-red, with many telangiectatic vessels which are not always easy to recognize. The eroded centers are covered with a whitish or yellowish membrane which is more or less adherent. When the lesions are isolated there is a decided resemblance to either aphthous stomatitis or to herpes. These alterations are similar to the oral manifestations in systemic lupus erythematosus, and in occasional instances, especially when the efflorescences are isolated, syphilis may be suspected.

In some cases the lesions may be deeply ulcerated. It is probable that this is owing not to any inherent attribute but more likely to secondary complications, such as superimposed infection. When such areas heal there are formed whitish depressed scars of variable size, up to that of a pea or larger, and such changes should not be confused with the leukoplakia-like alterations to be described in the next paragraph.

6. *Whitish Flat Areas* (*Leukoplakia-Like or Resembling Lichen Planus*). In my view this is one of the most important alterations found in the oral cavity in dermatomyositis. It has been observed by many investigators, myself included. Such changes are seen, especially on the cheeks, tongue and palate, as small areas, the size of a pea or larger, generally white or slightly yellow, with considerable resemblances to leukoplakia. However, in 10 cases of dermatomyositis Schuermann [11b] failed to observe this lesion. In a review of the literature this investigator, impressed by the apparent restriction of this lesion to men in advanced life, concluded that it represented ordinary leukoplakia. This view cannot be accepted for the following reasons: (*a*) whereas most cases concerned men, a few instances occurred in women,[42] one of whom was a girl of 21; (*b*) in some instances the lesions were found in young persons.[31, 42, 43] For example, in one case under my observation [10] such patches were noted on the tongue in a young man who did not smoke and in whom syphilis could be definitely excluded; (*c*) these

lesions are capable of rapid spontaneous involution, as occurred in the aforementioned patient; (*d*) the favorite sites for leukoplakia, especially the angles of the mouth, are not affected; (*e*) the appearance of these lesions may not be limited to simple whitish areas, but in addition erythematous puncta and telangiectasia may be superimposed.

Often the whitish areas are also arranged in the form of striae, lines or an irregular network, with considerable resemblances to lichen planus or lupus erythematosus. One or two examples recorded in the literature may well have been instances of lichen planus-like eruptions following the ingestion of arsenic, but in the vast majority of instances this factor can be safely eliminated from consideration. Each case must, therefore, be individualized in an effort to evaluate better this type of enanthem.

It is probable that the simple whitish lesions represent areas of localized hyperkeratosis analogous to those seen in relation to the proximal nail folds, which in the former situation are colored white, in the latter yellow, owing to anatomical peculiarities.

Subjective Symptoms. Involvement of the mucous membranes is often associated with subjective complaints that may be not only disturbing but also serious. It is important to stress, however, that some of the symptoms may be dependent more directly on concomitant disease in the deeper tissues, for example, the muscles.

Increased salivary flow with its attendant phenomena is observed chiefly in cases showing ulcerated areas in the mouth or intense edematous infiltrations accompanied by oozing of the parts. This symptom may be caused alone or may be intensified by the simultaneous presence of disease in the muscles of swallowing, so that part of the secretion is exteriorized instead of being swallowed. In occasional instances the breath may be extremely fetid.[14, 44] This is especially apt to occur when there is bleeding of the gums.[45]

Xerostoma or dryness of the mouth is less commonly encountered. The mucous membrane of the mouth may be the site of a generalized bright erythema, whereas in other cases this symptom appears in the absence of objective signs. For the most part the precise cause of this manifestation is obscure, and there is no evidence that a deficiency of any of the vitamins is responsible. It is a phenomenon worthy of further study.

Difficulty in swallowing is often caused by the various lesions in the mucous membranes, especially those near the posterior aspect of the mouth. Rarely involvement of the tonsils plays a part. More important and probably more common than these as a cause of this symptom is the occurrence of muscular disease in the pharyngeal and perhaps other small muscles. This complaint is always to be regarded apprehensively owing to the danger of bronchopneumonia. In the occasional case in which recovery takes place despite muscular disease, it is likely that the alterations in the muscles were relatively mild in type. The interference with feeding, often a real problem in therapeutics in these patients, may be enhanced by involvement of the deeper tissues in the cheeks, which provide an additional obstacle to opening

the mouth and swallowing. Chewing of food is often impaired owing to the painful tension on the muscles concerned in this act.[46]

Hoarseness is occasionally observed in dermatomyositis, and it arises from a variety of causes. Among these are involvement of the posterior portion of the throat by inflammatory or edematous infiltrations and similar changes in the larynx or in its muscles. Singly or combined, these may initiate the symptom or intensify it. Laryngeal edema of a high grade is an occasional cause of death.[41] In some cases the voice takes on a peculiar husky quality,[47] and sometimes the speech is slow and monotonous. It is apparent that these symptoms may lead to confusion with a host of other diseases, such as myasthenia gravis, scleroderma, etc.

Pain in the mouth is generally owing to the presence of ulcerated areas or localized edematous infiltrations. A common site is the tongue, and here the symptom may occur as a result of involvement of the overlying mucous membrane, edema of the deeper parts of the structure or actual parenchymatous disease. Inability to protrude the tongue [48] from out of the mouth is a not uncommon occurrence. Struppler [41] observed an instance in which a swollen and painful tongue was the probable site of referred pain to the neck, but more commonly pain in the neck is owing to involvement of the deep pharyngeal or sternocleidomastoid muscles.

On the whole, the symptoms caused by the lesions in the oral mucous membranes are analogous to those encountered in many other diseases affecting the mouth.

Prognosis of Lesions in the Oral Mucous Membranes. V. Livonius,[3] analyzing the records of 26 cases which showed involvement of the mucous membranes and in which the eventual outcome was known, found that death occurred in 12, or about 50 per cent of this group. An interesting point in this analysis was the practically invariable fatal outcome in those beyond the age of 50 years. These data did not impress Schuermann,[11b] for he noted a similar incidence of death in patients without involvement of the mucous membranes. Although this is true for the cases collected by Schuermann, it is unwise to accept the implications of this point of view. In mild examples of disease in the oral mucous membranes, the prognosis is probably not appreciably worsened. When these manifestations are more pronounced, especially in elderly persons, this must be regarded apprehensively owing to the possibility of a superimposed aspiration bronchopneumonia arising directly or as a contributory factor. The simultaneous occurrence of disease in the small muscles of the pharynx, etc., worsens the prognosis, although in occasional instances recovery may take place nonetheless.

Lips. The lips are sometimes sites of lesions in dermatomyositis. The most frequent manifestation is swelling of the parts, varying from a mild degree to the formation of projecting masses of tissue.[49] Digital pressure may cause pain, and this is especially likely to occur when the underlying muscles are implicated. Associated with the swelling there is often a superimposed redness or the erythema may appear alone, generally as bright red

to dusky red areas,[50] occasionally in the form of marmorization. When exudation is more intense, vesicles are sometimes seen and these may occur as crusted points. Ulcerations, the counterpart of those found in the oral cavity, are occasionally observed on the lips.[10] As in the case of the oral mucosa, grayish-white streaks or even atrophic spots may be seen, although less commonly. Aside from the swelling which is generally greater than that in systemic lupus erythematosus, these manifestations are differentiated with difficulty, if at all, in these two diseases. As a rule, the changes in the lips, consisting of telangiectasia, erythema and varying degrees of atrophy, are more apt to be found in all forms of lupus erythematosus. The similarities to lichen planus of the lips may be mentioned in passing.

Tonsils. Symptoms referable to the tonsils are sometimes encountered. These may occur at onset or during the course of dermatomyositis. Schuermann [11b] recorded an instance in a girl of 12 in whom there were periodic swellings and redness of the tonsillar regions, and he was inclined to view this phenomenon as being more than a simple tonsillitis. In Bruce's [51] second case the patient had, at onset, a slight sore throat accompanied by swollen cervical glands and a temperature of 103.5° F. In some cases there may be localized ulcerations, generally unilateral. Sheldon, Young and Dyke [52] reported one such example and noted, further, that there was no corresponding gland in the angle of the jaw. In still other patients the history seems to have indicated the occurrence of attacks of angina preceding the appearance of the more typical manifestations of dermatomyositis. It is of course difficult to be certain in such instances that this was actually caused by tonsillitis, for there are many other causes of sore throat in dermatomyositis.

On the whole, it appears that involvement of the tonsils, which occurs only occasionally, produces no signs or symptoms permitting differentiation from other diseases. It is still a question whether this is owing to a simple banal tonsillitis or is the result of inflammatory changes caused by dermatomyositis.

Conjunctiva. A few instances of dermatomyositis have shown injected conjunctivae due chiefly to dilated capillaries, the equivalent probably of the telangiectases in the skin. Sometimes this causes a dark bluish-red appearance, especially in the palpebral parts. In rare cases there is a degree of blepharitis,[53] with discharge at the angles of the eyes, uncommonly tearing and photophobia.

The injected appearance of the palpebral portion of the conjunctiva is more often encountered in systemic lupus erythematosus, whereas in dermatomyositis it is not an especially important manifestation. Solid plaques of atrophy in this part of the conjunctiva are occasionally found in lupus erythematosus of the discoid atrophic form, but these have never been seen in dermatomyositis.

In an occasional case there may be pain in the upper lids on digital pressure, which is generally owing to disease in the muscles, especially the orbi-

cularis oculi.[54] In rare instances paralysis of the extra-ocular muscles may cause varying grades of ptosis or strabismus.

Nose. In addition to the various changes mentioned previously, there may be isolated edema of the nasal mucous membrane [11b] and the lower turbinates [55] may be swollen. In Potain's [56] case the presence of an ulceration in the nasal cartilage was the chief basis for the diagnosis of glanders.

(2) *Manifestations Associated with Disease in the Muscles and Subcutaneous Tissues.* Dermatomyositis is generally regarded as a disease in which the muscles are chiefly affected, but often the subcutaneous tissue is simultaneously involved. In most cases it is relatively easy to differentiate the manifestations caused by muscular disease. In other instances this is more difficult and, for this reason, both structures are considered here jointly. Whenever possible, an attempt will be made to show the respective influence of each.

a. Edematous Infiltrations. The frequent occurrence of edematous infiltrations produces features that are distinctive, yet at the same time analogous with those found in other diseases. Sometimes this obscures other striking manifestations and must therefore be dissociated from them.

The edematous infiltrations affect large tracts of the limbs, chiefly in relation to the muscular masses although this is not always apparent. The clinical features often seem to depend upon the stage of the illness, the depth of the extravasated fluid and perhaps other factors. Early in the course the infiltration may be soft and pitting in type, later, firm and indurated, sometimes lardaceous. However, there seems to be no special rule, for the affected areas may show a doughy hardness from inception whereas in other cases the infiltration may be minimal and even apparently absent. In nearly all instances of dermatomyositis, especially when the edematous element is pronounced, there is associated an intense degree of pain, and this painful edema is one of the outstanding features of this disease. Often the overlying skin shows varying degrees of erythema and even a hemorrhagic component, but these manifestations may be absent or irregularly distributed.

If the edematous infiltrations involve large portions of the limbs, it is the rule to find that the areas overlying the joints are spared or affected minimally. This feature is a means of differentiating the edema of dermatomyositis from that of heart failure, save for those uncommon instances in which the former disease is accompanied by diminution in cardiac reserve. Moreover, the edematous infiltrations in dermatomyositis seem not to produce the hide-bound tightening of the skin directly overlying such joints as the wrists, ankles, etc., a feature that appears to differentiate this disease from diffuse progressive scleroderma.

The edematous element may be inconstant in the sense that such infiltrations may be conspicuous in one portion of the limbs or elsewhere and relatively inconspicuous in other parts of the same or other limbs. The latter may even at this time have reached the stage of evident atrophy of the musculature. In the latter case, also, the element of pain is elicited best by deep

pressure on the atrophic muscles themselves, whereas in the former, a slight amount of pressure on the underlying tissues is all that is required to bring out evidence of pain. When the edematous infiltration is pronounced, it is often possible to show that the degree of pain on digital pressure increases as one proceeds from the skin to the subcutaneous tissue, and, finally, to the muscles themselves. In many cases lying in bed or turning from side to side is sufficient to provoke agonizing sensations, so that patients generally lie immobile and can hardly endure the weight of bed sheets. This picture of severe pain is the classical one described in texts, but there are many instances in which the edematous infiltrations and the painful element are minimal, even absent. Despite this, the muscular masses may progress toward atrophy. The latter course of events is seen especially in so-called poikilodermatomyositis which, as I have stated before, seems to be but a variant of ordinary dermatomyositis.

A. Phenomena Associated or Seen With Edematous Infiltrations. 1. *Sign of Peau d'Orange.* In occasional instances of dermatomyositis the edematous collections produce elevations of the skin surrounding the hair follicles, while the latter act as though they were anchored in situ, thus causing an exaggeration of the follicular openings with deepening of their apertures. This phenomenon, to which the above name has been assigned because of its resemblance to orange peel, is seen in many conditions involving an extensive infiltration of edematous fluid directly in the upper part of the skin. It is equivalent to the appearance seen in cancer of the breast in which it is caused either by a tremendous infiltration of cancerous tissue especially in the lymphatics or, according to Handley, by perilymphatic fibrosis. This phenomenon may be encountered, for example, when the skin is infiltrated with procaine. It is often seen in myxedema tuberosum circumscriptum and may be observed in scleredema adultorum of Buschke, especially when the skin is pinched up, and occasionally also in ordinary diffuse scleroderma in the early stages. I have observed it several times in dermatomyositis as a localized manifestation, especially on the limbs. It is an interesting but nonspecific occurrence.

2. *Striae Atrophicans.* In some instances of dermatomyositis the edematous infiltrations invade the cutis and cause stretching of the elastica fibrils, probably to the point of rupture. This manifestation may become evident only after the edematous collections have been resorbed in large part, and the phenomenon is analogous to what occurs in obese persons who lose weight rapidly. The striae are seen chiefly about the areas of joints or near them, as in a case that I reported.[1a] It is probable that other areas may also be involved, for example, the abdomen, and in such a case there would be a close similarity with the striae found in association with pregnancy. The lesions in dermatomyositis seem not to be accompanied by hemorrhage and do not take on the bluish color seen so commonly in examples of "Cushing's syndrome."

3. *Calcification.* Calcific deposits are often found in the subcutaneous tissues in dermatomyositis, less commonly in the muscles. When the process is more extensive or secondary infection is superimposed, the cutis may also be involved.

These deposits are found chiefly in the subcutaneous tissues where they arise probably as a consequence of local damage to the panniculus adiposus. They are observed principally in the limbs, especially about the joints, including the smaller articulations. The lesions are also commonly found independent of these parts, for example, in the buttocks, near the axillae, occasionally near tendons, etc. These deposits may be localized in one or several areas, but sometimes they are so extensive as to resemble the clinical picture of a universal calcinosis. In some cases they are symmetrically disposed. There may be small or large conglomerated masses the size of a fist or larger, but in many examples a radiologic examination is essential for their discovery. Ordinarily the calcific deposits occur as firm, often irregularly infiltrated, deeply situated nodules whereas the overlying skin is unaffected or may become adherent to the main mass. As they increase in size the cutaneous tissue becomes implicated and there may appear thinning of the skin with bluish discoloration. When these deposits break through the skin, they exude a dry mushy material of pasty consistence. Healing occurs with the formation of a depressed scar. Occasionally abscesses form, probably as a result of secondary infection, and the evolution of these lesions is like that of a warm cutaneous abscess,[2] with formation of a suppurative focus exuding calcareous pus. Healing is featured by atrophic cicatrices.

Extensive deposits of calcium, especially those near or in relation to muscular masses, may cause interference with movement or play of muscles. Calcific masses occur also within the muscles themselves [32, 57] and are revealed, with great probability, by roentgen-ray examination. Rarely ossification apparently occurs, and in Bailey's patient [32] this was surmised on the basis of an increased opacity in the skiagram showing lesions near the greater trochanters of the femora. Exceptionally, calcific deposits may be observed in other organs. For example, Glück [43a] recorded the occurrence of calcification not only in the subcutaneous tissues, but also in the laryngeal cartilage. Whether the latter was definitely related to or coincidental with the process of calcium deposition in the subcutaneous tissues, it is difficult to be certain. In any event, this association needs further study.

When the process is universally distributed in the subcutaneous tissues, as in Randolph's case,[58] the clinical picture often resembles closely that of ordinary universal calcinosis. When the deposits are restricted chiefly to the muscles, the features simulate myositis ossificans.[59]

Subcutaneous calcification appears to be a nonspecific manifestation and may be encountered in a variety of diseases in which there is more or less involvement of this structure. Such lesions are met with, not only in dermatomyositis, but also in scleroderma, systemic lupus erythematosus, universal or localized calcinosis and probably other conditions. It seems un-

wise to deduce etiologic relations between diseases on the basis of this phenomenon, even though in some of the affections named the pathogenesis of these deposits may be similar or even identical.

Most observers agree that blood studies on the content of calcium and phosphorus reveal values within the range of normal. Sometimes the content of blood-calcium is actually diminished, although not to any striking degree. On the other hand, Petges and Petges [2] reported elevated values ranging from 13.5 to 15.5 mg. and deduced from this a definite relation to hyperparathyroidism. On the whole, however, the evidence presented, including the data in the cases under my observation, appears to be at variance with this view. Moreover, it is my belief that this type of evidence cannot be used to support an alliance between dermatomyositis and scleroderma.

4. *Loss of Weight.* Pronounced and often rapid wasting is frequently seen in dermatomyositis, this phenomenon generally being correlated with muscular disease. In some cases, however, implication of the subcutaneous fat contributes, partly at least, to an intensification of this phenomenon. During the stage of edematous infiltration and despite the rapid outpouring of fluid into the tissues, the weight may be below normal, and this becomes more manifest in cases showing improvement with resorption of the exuded fluid. Thus, in case 5 in a previous report [1a] wasting of the body became obvious following active diuresis.

At postmortem examination the subcutaneous fat may be absent,[60] atrophied,[1b] or replaced largely by fibrous tissue.[61]

It appears, then, that in many cases involvement of both the mucular and subcutaneous tissues contributes toward the rapid wasting so often seen in dermatomyositis and its congeners.

5. *Mucinous Deposits.* In a few cases of dermatomyositis mucinous material has been found in the deeper cutis when special stains were used. The status of this phenomenon remains unclarified, most observers believing that it represents a degenerative product. It is found in a wide variety of conditions, including true myxedema of the skin, myxedema tuberosum circumscriptum, occasionally scleredema adultorum of Buschke and a number of cutaneous diseases.[62] At present its occurrence is best regarded as a nonspecific phenomenon. The chemistry of mucin and the substances resembling it is in a state of flux. It is possible, although not certain, that the future may see means of differentiating these substances more satisfactorily.

6. *Electrocardiographic Changes.* There is reason to believe that in occasional instances of dermatomyositis the electrocardiogram may show low-voltage owing to the increased resistance to the electric current imposed by edematous infiltrations of the muscles, subcutaneous tissues and even the skin.[1b] Such changes therefore cannot be regarded per se as positive evidence of myocardial disease but require correlation with the clinical features as is the case in myxedema with its electrocardiographic findings. In one instance the electrical resistance was so great that tracings could not be obtained until later in the course.[63] Apparently such manifestations are va-

riable in their appearance and are seen only in an occasional example of dermatomyositis.

7. Total Protein in the Blood. The present knowledge concerning the chemical properties of the edematous infiltrations in dermatomyositis is fragmentary, and investigations along these lines are clearly indicated. There is reason to believe that occasionally the total protein in the blood may be diminished as a result of the widespread effusions [1b] and there is sometimes a tendency, although it is not especially striking, to a relative increase in the globulin fraction in the blood.[40c]

B. Topographical Influences. This section may now be completed with a more specific consideration of the changes produced in the clinical features in certain parts of the body owing to the pronounced degree of edematous infiltration. This is important for differential diagnosis.

1. *Face.* In a previous section a characteristic facies was described. It was stated then that this may be modified or obscured by the occurrence of accessory edematous infiltrations in the deeper tissues of the face. In the latter event it is often difficult to tell whether the principal changes are in the muscles primarily or in the subcutaneous tissues, and sometimes it appears that both are affected. The clinical features depend not only upon the degree of edematous infiltration in the more superficial tissues and in the extent of muscular involvement, but also upon the stage at which the patient is observed. This explains, in part at least, the variability of the descriptions found in the literature on this subject.

In these cases the face is bloated, shiny, and the skin feels stretched and tense. Usually a brawny, nonpitting edema is found, and the skin may be pinched up with difficulty, if at all, from the deeper tissues. In one case under my observation [1b] the edematous cheeks permitted pitting on digital pressure early in the course, whereas later these were sites of a firm indurated condition. As the lesion disappeared without residual sequelae, it seemed likely that the entire course of events could be explained on the basis of the type and degree of the edematous infiltration. Although the attributes of pitting on digital pressure and of lifting the skin in pliable folds are often characteristic and fairly constant in certain diseases, exceptions are apt to be encountered and the observer ought not to rely on hard-and-fast rules without knowing all the circumstances involved. Painfulness is also a variable symptom and may be replaced by a disturbing feeling of stiffness or tension in the parts.

When the edematous process in dermatomyositis is intense, the naso-labial folds are often almost or even completely obliterated. The tension on the tissues may be so great that the patient avoids talking or laughing.[64] All the other mimetic folds may also be obliterated, so that crying and smiling then make little change in the facial expression owing to the absence of normal wrinkling during the play of features.[19, 43b, 65] Moreover, there may be difficulty in opening the mouth, an important factor in interfering with nutrition, although as a rule, the latter is caused chiefly by muscular involvement.

The foregoing data indicate that there may be considerable resemblance between the facial features of dermatomyositis and diffuse scleroderma, atypical amyloidosis, etc. Indeed, some observers have argued for an identity between dermatomyositis and scleroderma on the basis of such similarities. Yet, except in rare and incompletely studied cases, this differentiation is really not difficult. In dermatomyositis, for example, it is rare to find the facial phenomena induced by the "sclerotic" alterations seen in the average example of scleroderma, such as the typical pinched nose, almost beak-like, and the thin mouth with retraction of the skin away from the line of the teeth and the linear, often radiating fissures encountered especially on the upper lips. Difficulties in differential diagnosis arise only in exceptional examples of each disease when the surrounding tissues are secondarily implicated; in dermatomyositis, the subcutaneous tissue, in scleroderma, the muscles. In such instances, assuming that the clinical differentiation is beyond diagnostic acumen as far as the facial lesions are concerned, a close examination of the remainder of the course will generally permit resolution of the problem. A detailed study of the clinico-pathological differences between these diseases will be given in a succeeding publication.

2. *Dorsa of the Hands.* The dorsa of the hands are often sites of edematous infiltrations, generally but not always accompanied by erythema of the affected parts. These infiltrations are similar in principle to those described on the limbs and face and show the same variable features already described. When the swellings and erythema are related to the tendinous structures and soft parts near the joints, for example the wrists, the observer may interpret this to mean involvement of the articulations. I have not seen in dermatomyositis the equivalent of the "frozen" wrists such as are commonly encountered in scleroderma. In some instances the edema is firm and doughy, interfering with closure of the hands and in such circumstances the resemblances to myxedema of these parts may be considerable.

3. *Abdominal Region.* Occasionally the musculature and, perhaps also, the subcutaneous tissues over the anterior abdominal wall are affected by edematous infiltrations showing the same features already detailed.[1b, 47, 66] Such manifestations may give rise to excruciating pains, and, unless interpreted properly, may be confused with intra-abdominal pathologic changes ("acute abdomen"). In cases involving large tracts of the abdomen, there may be resemblances to panniculitis of the abdominal wall.[67]

b. Rashes or Cutaneous Changes in Relation to Muscular Masses. In some cases of dermatomyositis it is difficult to tell whether the cutaneous manifestations represent part of a widespread exanthem or whether these are more directly related to changes occurring in the deeper tissues, such as the muscles. In this section the discussion will be restricted to those instances in which the cutaneous manifestations seem to be related to disease in the deeper parts, as the muscles, and an attempt will be made to explain the inclusion of these appearances under a variety of titles.

It may be stated at the outset that examples of this disease in which the eruption is restricted to obviously affected deeper tissue are generally recorded under the title of polymyositis. There appear, however, to be transitions between some of these cases and the variety showing the characteristic exanthem.

1. The edematous infiltrated and doughy muscular masses considered as typical of polymyositis (or dermatomyositis) are often surmounted by erythematous discolorations of variable extent and distribution. Where the erythemas are widespread or in the form of large tracts, these appearances generally go under the name of erysipelatoid redness, owing to the more or less vague resemblance to erysipelas of the limbs. Such cases have been recorded by many observers.[68] These erythemas may also be transitory, relatively pale or speckled in appearance, slightly scaly, patchy or irregular in distribution, and may reveal minute capillary hemorrhages at the peripheries of patches or within them. These lesions are generally found on the extensor aspects of the limbs, but also frequently on the flexor surfaces, and occasionally in relation to the muscles of the trunk and other parts.

In other instances the patches assume a violaceous hue [68a] or are colored a deep red. When such lesions are of limited size and are associated with pain in the underlying muscles, they may resemble closely erythema nodosum. The designation of phlebitis may be applied to such changes when they seem to lie in the line of veins. The term urticaria has occasionally been utilized in some cases for pale rosy, more or less transitory edematous infiltrations when the author really meant that these infiltrations were urticarial in type (major component being fluid in the tissues).

The purpose of this discussion, then, is to point out the necessity of designating accurately the cutaneous appearances, so that the literature may be freed, so far as possible, from extraneous names for manifestations readily explained on clinicopathologic grounds.

2. *Hypertrichosis.* Sometimes hypertrichosis of a localized type may be observed,[1b, 11b, 31, 69] chiefly in relation to the limbs, occasionally elsewhere. The occurrence of this curious phenomenon has led some observers to attribute it to an endocrine origin. In my view this manifestation arises from local causes, although the precise mechanism is as yet obscure.[1b] It is encountered in areas the sites of evident involvement of the deeper tissues accompanied often, although not always, by a degree of erythema in the skin. The inflammatory element, whether collateral or otherwise, seems to stimulate growth of hair, possibly through the medium of an increased blood supply or the presence of edematous fluid. It is of interest that a similar phenomenon has been noted occasionally in examples of myxedema tuberosum circumscriptum, and it appears that the mechanism may be similar, if not identical, in the two conditions.

3. *Tendon Streaks.* A few observers have described erythematous streaks that apparently ran along the course of tendons, especially those of the forearms and hands.[17, 43a, 51] Undoubtedly involvement of tendons occurs in

dermatomyositis and is one of the causes of contractures. It seems reasonable to infer that the cutaneous manifestations of this type may be related in some way to disease in the tendons, although in some cases these appearances seem to behave as though they were part of an exanthem. As this subject has received but scant attention, the matter must remain sub judice.

Skin-Muscle Relation

The association of cutaneous and muscular disease in the same patient is the fundamental background of the average example of dermatomyositis. It is not surprising, therefore, that observers have been deeply interested in the relation between these structures in this disease. Two principal views exist in this regard: (1) the eruptions represent a "collateral inflammatory element" in the sense of Tendeloo,[11a] that is to say, the cutaneous changes are secondarily and completely dependent on the subjacent muscular disease [70]; (2) the eruptions arise independently of alterations in the deeper tissues. In my view there is truth in both contentions, and it appears that each side has concerned itself only with its own particular observations. Sometimes the distinctions seem academic, but that arises chiefly because our present knowledge restricts definite decisions. It will be my purpose now to discuss the fundamentals of this controversy in greater detail.

1. A few observers, especially Schuermann,[11b] have stressed the point that an interval of time often occurs between the appearance of the rash and clinical evidence of muscular disease. There are many cases in which the cutaneous lesions seem to appear some weeks, months, perhaps even years, before muscular phenomena are recognized. I can substantiate this point, but only in a general way, for there is at least one obstacle to its complete acceptance. Although this interval of time exists in a clinical sense, it is not at all certain that the muscles have actually been free of pathologic changes from the onset of the illness. This is the crucial point in the discussion, namely, that in the early stages when the eruption is conspicuous, the diagnosis is often overlooked and such instances are generally recorded as systemic lupus erythematosus, etc. O'Leary and Waisman [80] are inclined to believe that "in cases in which the onset is associated with a dermatosis subclinical muscular inflammatory changes are already present." Having seen a fairly large number of cases in the early stages, it seems to me that if the muscles were carefully palpated, evidence of their involvement would be forthcoming, certainly in a larger percentage than is generally recorded in this phase of the disease. However, it requires thorough search since only a few muscles may be affected at this time, and for this reason a biopsy specimen of muscle may fail to show alterations unless the proper site happened to have been chosen for this examination. On the other hand, there is reason to believe that our present knowledge of what are to be regarded as positive findings in biopsy specimens is not entirely clear. That is why a clinical approach with emphasis on the early cutaneous lesions is important.

2. Frequently there is a disproportion between the severity of the muscular changes and the cutaneous manifestations. Much weight has been laid on this point. However, this may be a fallacious argument in view of our lack of knowledge regarding the actual state of the musculature in such examples. It has long been known, for instance, that severe muscular changes may be encountered in patients with relatively little or even no symptoms referable to this tissue.[11e, 42a, 43a] It has been suggested [1b] that in such cases the edematous element, which is so closely associated with the complaint of pain, may be minimal in extent. The difficulties are further enhanced by the observation that the muscles may appear grossly normal, yet may present definite minute anatomical alterations.

3. Superficial lesions are often observed in areas devoid of underlying muscle, as for example, in the skin, over the knuckles, and in the mucous membranes on the hard palate and other parts. This is one of the best arguments for the dissociation of the exanthem and enanthem from disease in the muscles, but this conclusion holds mainly for the cutaneous and mucous membrane lesions described under the headings of exanthem and enanthem.

4. Many small muscles may be affected in areas in which there is no overlying skin, for example, the palatal muscles, diaphragm, etc. This argument has only restricted value.

5. The occurrence of cases in which the cutaneous lesions appear to be limited exclusively to sites of involved muscle affords evidence that in these instances, at least, a direct skin-muscle relation can be postulated reasonably. In these patients, however, the eruptions are generally not of the exanthematic type, but consist of dermatoses such as have been described at the head of this section. The few examples of tendon streaks may be mentioned here, but their pathogenesis must be left sub judice until additional data are forthcoming.

6. Finally, there seems to be a close anatomical relation between the blood supply of the muscles and the subcutaneous tissues, possibly also the lower portion of the cutis. However, information on the precise nature of this relation is surprisingly fragmentary.

From the data at hand, it is my belief that the alterations described in the category of exanthem and enanthem are best interpreted as phenomena occurring simultaneously and independently of the muscular changes, although both the skin and muscles are affected by the same etiologic factor. The other eruptions mentioned in this section seem to be closely associated with disease in the muscles and are apparently dependent upon the latter. When the affection strikes both systems with particular violence, it may be difficult to establish the nature of the relationship.

(3) *Miscellaneous Cutaneous Manifestations.* The eruptions mentioned in this section generally have but little diagnostic importance and are often a confusing element. In many of the published accounts such dermatoses have been cited as important and essential lesions in dermatomyositis, but it

is my belief that this is not the case. Few observers seem to have considered these eruptions critically.

a. Miliaria Crystallina. This occurs occasionally in patients exhibiting abundant sweats in this disease. It is probable, however, that the importance of profuse sweating, originally stressed as an integral part of the symptomatology, has been exaggerated.[30, 1b] Its incidence, especially the severe bouts of sweating, appears to be much lower than the early reports in the literature indicate. Nevertheless, it does occur and is seen chiefly in severe cases of dermatomyositis requiring hospitalization, particularly those with high temperature. In some instances it seems to take the form of a "vasomotor" manifestation of unexplained nature. In such circumstances it becomes a phenomenon worthy of further study. Of itself it has no great value in differential diagnosis owing to its banality.

b. Roseola. In rare instances a small maculopapular eruption, occurring chiefly on the trunk as discrete spots, has been designated as a "roseola." Nearly all such examples have concerned cases in which the diagnosis of dermatomyositis was doubtful. Indeed, there is reason to believe that such instances may have been generally examples of trichinosis, a disease in which a roseola-like eruption is far more commonly encountered. In any event, the appearance of such lesions in the skin in dermatomyositis, if authenticated, is exceptionally rare. No such case has come under my observation and the more recent literature is completely silent on the point.

c. Herpes. Both herpes simplex and zoster are occasionally seen in dermatomyositis, also in systemic lupus erythematosus. These eruptions appear to possess doubtful value in differential diagnosis or prognosis. It is not rare to find a herpes simplex in association with a complicating pneumonic process in these diseases.

d. Urticaria. This is an uncommon manifestation in dermatomyositis.[71] In most instances the descriptions furnished would lead the critical observer to believe that these lesions were probably of the nature of more or less transient edematous infiltrations in the deeper tissues, such as the muscles and subcutaneous tissues. It may be mentioned, in passing, that true urticaria is an occasional accompaniment of trichinosis.

e. Erythema Nodosum. What applies to urticaria holds pari passu for erythema nodosum. In both, also, the incidental factor of drugs must also be eliminated as a possible cause, especially in these days of widespread use of sulfathiazol.

f. Scarlatiniform Exanthem. A few cases have been described in which the eruption at onset was diagnosed either as scarlet fever or a scarlatiniform exanthem.[71, 72] It is probable that some of these, at least, represented the ordinary unrecognized eruption of dermatomyositis in a somewhat pronounced form. Whether the appearance is seen early or late in the course, it is always advisable to eliminate the possibility of other etiologic factors, especially drugs. Each case therefore requires individual study. On a

comparative basis trichinosis is more apt to show this type of dermatosis during its course. The rarity of this eruption in dermatomyositis and its obscure status do not warrant a place for it among the cutaneous manifestations of this disease, unless more convincing data are recorded in the future.

g. "Erythema Multiforme." 1. *Erythema Marginatum.* I have encountered two cases of dermatomyositis in which there were large plaques of marginated erythema chiefly on the limbs. In these instances the diagnosis of rheumatic fever had been originally suggested because of the eruption and the clinical features of "articular" pains, fever, sweating and, in one case, a high antistreptolysin titer, etc. Both concerned young persons in the second decade of life. Though there were some resemblances to the typical erythema marginatum rheumaticum, the eruption in dermatomyositis showed the following differences: (1) the limbs were the principal sites, the trunk being excepted. This is contrary to what is generally seen in the rheumatic type, though, it must be admitted, such localization does not entirely exclude the rheumatic variety; (2) more important, the individual marginated plaques in dermatomyositis remained visible in the same state for weeks or even months, whereas the cutaneous lesions in rheumatic fever are featured by transiency in the individual lesions.[75] This fundamental difference in behavior was helpful in placing the proper labels on these cases.

Undoubtedly such cases have been classified in the past as "muscular rheumatism," but the clinical course of the disease warrants separation of these two examples of dermatomyositis from the obscure syndrome encompassed within the term "muscular rheumatism."

2. *Vesiculo-Bullous Erythema Multiforme.* The occurrence of scattered vesicles and bullae, sometimes of hemorrhagic type, in cases of dermatomyositis has often obscured recognition of the essential diagnosis. It has been pointed out [39] that the diagnosis of erythema multiforme, unless qualified in such a way as to designate a particular disease, is simply a morphologic description. There are times when our present knowledge does not permit more accurate classification of "erythema multiforme" but this difficulty will be overcome in future, as observers attempt to correlate such eruptions with the systemic manifestations.

h. Cutaneous Hemorrhages. Irregularly distributed purpuric spots, less commonly petechiae, are occasionally found in dermatomyositis. As in many other diseases, the lower limbs are often sites of such manifestations. The lesions are generally seen late in the course, occasionally early. In some instances there is an associated moderate grade of thrombocytopenia,[11b, 11b] but, as a rule, the relation of these hemorrhages to the hematologic formula, including the tourniquet test, bleeding time, coagulation time and clot retraction, is inconstant. There seem to be no clinical features by which these hemorrhagic manifestations can be distinguished from those seen in a host of other diseases.

Hemorrhages may also occur secondarily into other types of lesions, such as isolated vesicles or bullae, etc.

On the whole, these manifestations add a confusing element to the clinical picture and are best remembered in a negative way.

i. Ulcerations in the Skin. These appearances arise in a number of ways:

a. Pressure sores (decubitus ulcers) are occasionally observed over the sacrum and other points of pressure.[74, 69c] The factors contributing to their origin are the patient's immobility in bed for reasons mentioned and the probable poor local state of the tissues implicated. These ulcerations are to be regarded apprehensively owing to the possibility that they may serve as a focus for a complicating bacteremia,[74a] although healing may occur spontaneously.[1a]

It is more common to observe ulcerations in scleroderma, especially over articular areas. This is probably caused by the pressure of the hide-bound skin stretched tightly over the deeper contractured joints and the added factor of a deficient circulation to these parts. More rarely, calcific deposits in the subcutaneous tissues or in the skin may break through to the outside.

b. The occurrence of ulcerations in the skin secondary to the pressure of calcific deposits in dermatomyositis or to superimposed infection of these foci has been previously mentioned, and likewise, the relatively common superficial erosions in the oral mucous membranes and the rare ulcerations in the nose and other parts.

j. Livedo Reticularis. In an instance of dermatomyositis under my observation there appeared, as a sequel several months after the acute phase had been weathered, the cutaneous phenomenon classed as "livedo reticularis or racemosa." The lesions affected both the upper and lower limbs. Originally regarded by Ehrmann [75] as a manifestation of syphilis, other observers began to record its occurrence in association with a host of other diseases. In recent years, however, this eruption has been stressed as a manifestation of periarteritis nodosa.[76] Without discussing the subject in any detail, it is my belief that these lesions represent a nonspecific eruption occurring in association with many diseases. The question of whether the pathogenesis of livedo reticularis is the same or similar in all cases must be left open at present.

Summary

A detailed classification and discussion of the cutaneous and mucosal manifestations of dermatomyositis are given in terms of a clinicopathologic correlation. Throughout the presentation an attempt has been made to indicate the essential differences from the eruption seen in systemic lupus erythematosus despite the many resemblances. There is a typical dermatomyositic facies which may, however, be obscured by a number of factors. Under the appropriate sections, also, reasons are given for the resemblances of dermatomyositis to such diseases as trichinosis, glomerulonephritis, sinusitis, pellagra, Addison's disease, scleroderma, scleredema adultorum, a spe-

cial type of panniculitis, acrodermatitis chronica atrophicans, epidermolysis bullosa and many other affections. In most instances the differential diagnosis is discussed fully; in others, due to limitations of space, a few essential points of difference are mentioned. A detailed analysis of the edematous infiltrations seen in dermatomyositis is given, together with a discussion of a number of phenomena associated or seen with these infiltrations. The nature of the skin-muscle relationship is considered and an attempt is made to clarify some of the obscurities involved in this fundamental subject.

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MULTIPLE TESTS OF HEPATIC FUNCTION IN GASTROENTERIC MALIGNANCY; THE VALUE OF BROMSULPHALEIN, HIPPURIC ACID AND THE VAN DEN BERGH REACTION IN DETECTING HEPATIC METASTASIS, WITH AN EVALUATION OF NORMALITY OF THE HIPPURIC ACID TEST *

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From time to time throughout the past years communications have appeared which have indicated that the prediction of the existence of hepatic metastasis was a possibility. In 1925 Rowntree and his associates [1] using phenol tetrachlorphthalein concluded that "in the absence of clinical evidence of hepatic involvement the phenoltetrachlorphthalein test may furnish the only evidence of the existence of metastatic nodules in the liver." Positive tests were not obtained in all cases of metastatic involvement. Bargen and Rankin,[2] in 1930, felt that their results, using bromsulphalein and the van den Bergh test in carcinoma of the large bowel, were statistically indicative although again there were individual exceptions. In 1935 Wever, Althausen and Biskind [3] attacked the problem using the Rose Bengal test together with icterus index and glucose tolerance. In 33 cases of secondary hepatic neoplasm, 26 showed some degree of dye retention. The negative side of the problem, i.e., results in patients without metastasis, was not discussed. Meranze, Meranze and Rothman,[4] using the Bodansky alkaline phosphatase determination,[5] found an excellent correlation between elevated phosphatase levels and hepatic metastasis. Gutman, Olson, Gutman and Flood,[6] commenting on this work, agreed with its general validity but point out again that errors may occur in patients both with and without metastasis.

It was with this literature in mind that we decided to determine whether application of the hippuric acid synthesis to this problem would be of benefit. Accordingly this test was performed, together with the bromsulphalein determination and the quantitative indirect van den Bergh reaction, on a number of patients with malignant disease. The necessity for the use of multiple tests in the evaluation of liver function status and the fact that disorder of function may appear more evident in one modality than in another are well appreciated.

Material

The patients investigated were individuals who clinically and roentgenologically were thought, prior to surgery, to have malignancy of the

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stomach or the colon. We restricted ourselves to these sites of origin because such tumors are well known to involve the liver early by metastasis. No patients with palpable livers, jaundice, or any other evidence of either liver disturbance or metastasis elsewhere were included in our group. When metastases are described subsequently as present or absent this denotes whether or not they could be seen or felt by the operator several days later.

Method

The hippuric acid determinations were done as described by Quick,[7, 8] using the intravenous method. This was necessary since some of the patients were undergoing gastric aspiration in preparation for surgery at the time determinations were done. The studies were started before we were aware of the modification proposed by Weichselbaum and Probstein,[9] and it did not seem advisable to change our technic once we had started. However, we made use of their work by adopting as the solubility factor 0.0055 gm. per c.c. which is their average finding, rather than the 0.0033 originally suggested by Quick. It is possible that several of the cases with zero excretion actually would have shown some precipitation if salting out had been resorted to, although they obviously would have been quite low. Nitrogen retention was not present in those cases with low figures.

The bromsulphalein test of Rosenthal and White[10] is too well known to require any further description. It should be noted, however, that the 5 mg./kilo dosage was used throughout and that all determinations were made one-half hour after intravenous injection.[11]

The indirect quantitative van den Bergh reaction requires no comment.

Results

Table 1 shows the results on 25 consecutive patients with malignancy. Study of this table reveals several things. It is apparent that, although the bromsulphalein test is of considerable value in the prediction of metastasis, the correlation is not perfect. We did not anticipate normal tests invariably in the absence of metastasis, since there is no reason why preëxisting liver damage could not cause an abnormal test in the absence of metastasis. However, at least two cases (12 and 15) showed metastasis with bromsulphalein excretion at normal levels.

The van den Bergh test proved of no value other than to exclude icterus chemically as had already been done clinically.

There is no correlation whatsoever between the level of hippuric acid excretion and the presence of metastatic hepatic lesions. It is true, though, that a complete absence of hippuric acid by the method used was in every instance associated with metastatic involvement (six cases). What did intrigue us, however, were the uniformly low levels of hippuric acid excretion which we obtained in this series. With three exceptions the results are below the normal of 1.00 to 1.40 grams of hippuric acid (following the

TABLE I

No.	Patient	Age	Sex	Site of tumor	Met. to liver	vdB units	B.S.P.	Hipp. Acid	Remarks
1	L.S.	61	F	rectum	No	0.2	5%	1.00	Normal hipp. acid
2	P.P.	51	M	hepatic flexure	No	0.3	5%	0.93	
3	E.J.	33	F	rectum	No	0.2	5%	0.87	
4	J.A.	62	M	stomach	No	0.3	5%	0.80	
5	P.G.	48	M	stomach	No	0.3	5%	0.79	
6	E.C.	55	M	stomach	No	0.2	5%	0.63	
7	A.S.	49	M	cecum	No	0.4	5%	0.62	
8	J.L.	53	M	stomach	No	0.3	5%	0.60	
9	G.W.	51	F	sigmoid	No	0.4	5%	0.54	
10	C.P.	57	M	stomach	No	0.2	5%	0.51	
11	H.G.	67	M	stomach	No	0.3	5%	0.44	
12	T.S.	68	M	cecum	Yes	0.3	5%	0.00	Single nodule in liver
13	B.W.	58	M	stomach	No	0.5	10%	1.08	Normal hipp. acid
14	J.L.	51	M	stomach	No	0.3	10%	0.91	
15	W.A.	42	M	stomach	Yes	0.75	10%	0.41	Small scattered nodules
16	M.S.	42	F	stomach	Yes	0.5	15%	0.87	Peritoneal implants; liver relatively free
17	B.M.	58	M	stomach	Yes	0.5	15%	0.51	Tumor adhered to liver, pancreas, spleen
18	J.R.	66	F	rectum	Yes	0.5	15%	0.39	Scattered nodules
19	H.W.	73	F	sigmoid	Yes	0.4	15%	0.00	Widespread
20	S.B.	40	F	transv. colon	No	0.2	20%	1.13	Normal hipp. acid
21	H.B.	72	F	stomach	No	1.25	20%	0.44	
22	A.L.	65	M	rectum	Yes	0.2	20%	0.00	Scattered nodules
23	B.M.	48	F	transv. colon	Yes	0.3	25%	0.00	Widespread
24	R.J.	66	M	stomach	Yes	0.3	30%	0.00	Widespread
25	L.L.	52	M	sigmoid	Yes	0.75	40%	0.00	Widespread

intravenous administration of 1.77 grams sodium benzoate) as suggested by Quick [7, 8] and confirmed in adults by Weichselbaum and Probstein,[9] Mateer, Baltz, Marion, and Holland,[12] and others.[13]

As a possible explanation of this, it occurred to us that the normal for this test had probably been determined on healthy young adults. It is also our experience that "normal" levels are almost always attained in the usual healthy youth. We could find no record, however, of the test's having been applied to individuals in the middle and late decades of life—to individuals who had no evidence of or obvious cause for hepatic damage. Therefore, we decided to apply exactly similar tests to a group of hospital patients of approximately the same age and sex distribution who did not have carcinoma, who had no obvious cause for or sign of hepatic disease or dysfunction, and who were essentially free of digestive complaints. As the accompanying chart shows, however, these patients suffered from various major illnesses and, although the outcome was favorable in the majority of instances, the patients at the time they were studied were moderately or severely ill. The results of this study are shown in table 2. It can be seen that, although in this group seven of the cases attain normal figures and several others are quite close to that level, at least 16 of the 25 patients showed a deficit in the synthesis and excretion of hippuric acid of a degree which is ordinarily con-

sidered to signify impaired hepatic function. This is particularly striking inasmuch as 23 of the 25 patients had a completely normal excretion of bromsulphalein. Although we do not by any means wish to compare procedures evaluating dissimilar functions, it is our common experience and that of others that clinically significant liver damage is very frequently accompanied by a reduction in bromsulphalein excretion. In none of these cases was a significant elevation of the van den Bergh test encountered.

TABLE II

No.	Patient	Age	Sex	Diagnosis	B.S.P.	vdB	Hipp. Acid	Remarks
1	L.K.	28	F	Acute arthritis, type undetermined	5%	0.1	1.33	Normal hipp. acid
2		43	M	Acute pyelitis	5%	0.4	1.23	Normal hipp. acid
3	J.C.	51	M	Pneumonia Pneumo. I	5%	0.5	1.23	Normal hipp. acid
4	M.P.	26	M	Acute rheumatic fever	5%	0.2	1.22	Normal hipp. acid
5	C.L.	33	M	Gon. arthritis, acute	5%	0.2	1.20	Normal hipp. acid
6	B.J.	43	F	Acute rheumatic fever	5%	0.3	1.18	Normal hipp. acid
7	P.C.	53	M	Sarcoid	5%	0.4	1.13	Normal hipp. acid
8	E.W.	61	M	Auricular fibrillation with mult. emboli	5%	0.2	0.98	
9	I.Z.	49	F	Nephrosclerosis	5%	0.2	0.96	No nitrogen ret.
10	U.B.	47	M	Subacute bacterial endocarditis	5%	0.3	0.85	
11		56	F	Pneumonia conv.	5%	0.3	0.85	
12	L.B.	46	F	Subacute bacterial endocarditis	5%	0.2	0.73	
13	C.W.	59	M	Active rheumatoid arthritis	5%	0.3	0.67	
14	M.W.	68	F	Pneumonia Pneumo. I	5%	0.4	0.58	
15	O.W.	42	M	Coronary occl. No failure	5%	0.5	0.57	
16	E.G.	57	F	Acute rheumatoid arthritis	5%	0.3	0.55	
17	C.H.	61	F	Pneumonia Pneumo. V	5%	0.3	0.53	
18	C.J.	59	F	Neurologic dis. with muscle atrophy	5%	0.2	0.53	
19		51	F	Arthritis acute type undeterm.	5%	0.3	0.48	
20	P.R.	55	M	Coronary occl. No failure	5%	0.3	0.44	
21	P.B.	39	M	Asthmatic bronchitis, bronchopneumonia	5%	0.3	0.38	
22	L.T.	41	F	Avitaminosis due to inadequate food intake	5%	0.4	0.32	
23	M.D.	29	M	Polycystic kidney with impending uremia	5%	0.2	0.32	
24	E.T.	54	M	Pneumonia no type	10%	0.2	0.45	Mod. alcohol ingestion
25	I.S.	60	F	Bronchiectasis with bronchopneumonia	15%	0.2	0.00	Had had antiluetic treatment

It is interesting to speculate on possible explanations for these consistently low figures of hippuric acid excretion. First, it is considered possible that the procedure is not entirely a test of liver function. Best and Taylor [14] state (without giving evidence) that formation of hippuric acid from benzoic acid and glycine takes place in the kidneys as well as in the liver. The kidneys are known to be principally concerned with this function

in the dog at least. Although none of the patients tested had an abnormal degree of nitrogen retention, it is still conceivable that renal damage may have influenced the results.

Although the test is performed with the patient fasting or after partaking of only a light meal, it seems obvious that the patient's nutritional state at the time of testing may modify the results—this in spite of the body's known ability to synthesize glycine. We have indeed found this to be true in several cases—the amount of acid obtained rising as a dehydrated and malnourished individual with a gastric carcinoma is hydrated, transfused and prepared for surgery.

It may also be suggested that the low figures are, in fact, an expression of actual hepatic dysfunction and that this may indeed in some of the acutely ill subjects be a temporary thing. Haines, Magath and Power,[15] who investigated the hippuric acid test in thyrotoxicosis, have noted that "it seems probable that marked alterations in the test can occur because of functional changes in the liver that must be of short duration and temporary." It is certainly true that when patients with many of the diseases enumerated in table 2 are seen at the autopsy table, microscopic abnormalities are found in the liver.

Whatever may be the cause of these results, practically it is important to point out that they do not necessarily signify important primary disease of the liver. The normal bromsulphalein excretion encountered almost throughout table 2 is in line with clinical findings. Haines and his co-workers [15] also noted in their study that, although there was some correlation in hyperthyroidism between bromsulphalein retention and reduction of hippuric acid output, there were frequent exceptions, with a normal bromsulphalein and considerable reduction of hippuric excretion. They concluded, in addition, that the test was of little value in pre-operative determination of the patient's fitness for surgery in thyrotoxicosis. Whether the hippuric acid excretory level would rise toward that figure considered normal in many of those individuals in table 2 who made essentially complete recoveries from acute illnesses is something which at present we are not able to answer.

It becomes apparent from a consideration of these data that increased sensitivity in tests of hepatic function, which has been a prime desideratum of investigators in this field, can definitely be carried beyond practicable limits. Tests can become so delicate that insignificant or transient degrees of dysfunction are detected by them. In this way the result of the test loses its significance and the procedure fails as a diagnostic measure by drawing attention to the liver in undiagnosed disease, when this gland is not primarily or even importantly involved. Hepatic function tests of greatest value may be thought of as occupying a relatively narrow band of sensitivity with tests of less clinical value ranged on either side. The most highly sensitive tests, of course, may be of considerable value when used serially in recording progressive change in condition and prognosis.

It should be obvious that the statements and discussion above have nothing to do with those tests used in differentiating intra- and extrahepatic icterus.

Summary and Conclusion

Hippuric acid, bromsulphalein and van den Bergh tests were done on 25 patients with carcinoma of the stomach or colon who had no clinical evidence of metastasis. A correlation was found to exist between the presence of gross hepatic metastasis, as determined at subsequent operation and the degree of bromsulphalein retention, although individual exceptions occurred. No significant correlation was found between the presence of metastasis and the amount of hippuric acid excreted. However, in all six cases in which no hippuric acid was found metastases were present. The van den Bergh was not of diagnostic aid.

Owing to the uniformly low levels of hippuric acid excretion found in these cases of carcinoma, a second series of 25 patients of comparable age and sex distribution was tested. This latter group was composed of individuals who had no signs, symptoms, or good historic reason for hepatic damage but who were suffering from a wide variety of acute and chronic diseases. Sixteen of these patients showed lowering of the hippuric acid synthesis below the level considered as normal, although in 23 of the 25 cases the bromsulphalein excretion was entirely within normal limits. Possible explanations for this difference are discussed. It is suggested that extreme delicacy in tests of hepatic function may detract from their importance as diagnostic aids by too frequently giving abnormal results in cases in which liver damage is slight and is a relatively unimportant part of the general clinical picture. This in no way invalidates the serial use of the most delicate tests in following the course of liver disease and in so determining prognosis. Neither do the above statements apply to those tests used in the differentiation of intrahepatic from extrahepatic icterus.

This concept (that liver function tests can fail if too sensitive) is somewhat different from that usually held, in which it is felt that the failure of tests of hepatic function is primarily owing to their grossness.

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SOME EFFECTS OF POTASSIUM SALTS IN MAN*

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During the last few years both the physiologist and the clinician have discovered many new facts regarding the metabolism of potassium. Several factors have stimulated recent studies in this subject and among these have been the availability of accurate microchemical methods for the estimation of potassium in body fluids, the application of physiologic principles to the study of certain clinical syndromes, and a desire to establish more clearly the dividing line between the pharmacologic and toxic effects of potassium salts.

The problem of toxicity has been confused in the past by conflicting results obtained in two types of studies. The initial experiments of Blake [1] in 1839 revealed that the rapid intravenous injection of a potassium salt into a dog is quickly fatal. However, 40 years later, in 1881, Feltz and Ritter [2] injected a similar dose slowly, for example in 10 minutes, and no untoward symptoms developed. The latter result gave us a clue as to why relatively large doses of potassium salts have been given by mouth for many years without obvious toxic effects. As much as 40 gm. of potassium chloride have been ingested in one day by patients suffering from myasthenia gravis without toxic symptoms.[3] McQuarrie and coworkers [4] reported the administration by mouth of 48 gm. of the same salt daily to a patient who had acromegaly and hypoglycemia; no untoward effects occurred. Apparently osmotic and other factors acting within the lumen of the small bowel prevent too rapid absorption of potassium salts into the blood stream. The experiments of Winkler, Hoff and Smith [5] in the dog support such a point of view. Therefore, to ascertain the single maximal nontoxic dose of a potassium salt given by mouth to a human subject seemed to be a pharmacologic problem worthy of further study. We shall proceed to outline such an attempt in which normal volunteers were subjects and endeavor to follow the lead so ably given by Ringer and Murrell [6] in 1878 in their well-known experiments in the frog. Ringer interpreted their results as revealing that potassium salts in large doses had a toxic effect on the nervous and muscular tissues, but emphasized that they had a widespread toxic action on all "nitrogenous tissue."

Effect of Potassium on the Kidney

Our first objective was to determine the effect of a large single dose of a potassium salt on the renal clearance of potassium and inulin. Seven normal persons ingested 12.5 to 17.5 gm. of potassium chloride or bicarbonate and

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after absorption had occurred the clearances were estimated.* The routine procedure in these studies consisted in obtaining a control specimen of urine in the early morning, the ingestion of a given potassium salt in 6 to 25 per cent solutions, and then collection of hourly or half hourly specimens of urine. No food was taken in four studies, but to prevent epigastric burning in three a small breakfast was eaten just before ingestion of the potassium salt. This consisted of either two soft boiled eggs or a small portion of oat porridge and 50 c.c. milk. In order to have a satisfactory volume of urine for clearance studies 100 to 200 c.c. of water were ingested every half to one hour throughout the observations. The inulin clearance was determined after the intravenous injection of 100 c.c. of a 10 per cent solution of inulin containing 0.9 per cent sodium chloride, and the chemical determinations in the blood and urine were made according to Alving's [7, 8] method.

In five subjects the potassium clearance rose from the normal fasting level of 6 to 14 c.c.[9, 10] to 41 to 105 c.c., but that of inulin was within the normal range, 93 to 146 c.c. (table 1). During the clearance periods the concentration of potassium in the serum varied from 22 to 28 mg. per 100 c.c. Similar

TABLE I

Renal Clearances: Large Single Dose of Potassium Salt without Toxic Action

Subject (normal person) and surface area, sq. m.	Dose, gm.		Experimental period, minutes	Urine minute volume, c.c.	Plasma and serum clearance*			
	Potassium salt	Potassium†			Inulin	Potassium	Urea	Ratio of potassium to inulin
Ki. 1.97	12.5 $KHCO_3$	4.9	30	3.5	115	52		0.45
	9.5 KCl‡	5.0	67	2.6	143	58	67	0.41
Bu. 1.75	12.5 $KHCO_3$	4.9	31	14.8	137	105		0.77
Ke. 1.95	17.5 $KHCO_3$	6.8	30	2.8	134	41		0.31
Gr. 1.92	17.5 $KHCO_3$	6.8	30 30	3.2 2.9	93 115	49 44		0.53 0.38
Ro. 1.74	12.5 KCl	6.5	30	4.1	146	49	77	0.34
Mean					126	57		0.46

* Calculated as c.c. per 1.73 sq. m. per minute.
† 0.06–0.1 gm. per kilogram of body weight.
‡ Injected intravenously in ninety minutes.

* The potassium in the serum was determined by the method of Kramer, Benjamin and Tisdall, F. F.: A clinical method for the quantitative determination of potassium in small amounts of serum, Jr. Biol. Chem., 1921, xlvi, 339–349. This method in our hands has checked with gravimetric procedures. The precipitation by sodium cobalti-nitrite was allowed to proceed for 45 minutes at icebox temperature in order to obtain a good granular precipitate. If this and other steps are adhered to rigorously, the method is a satisfactory procedure. Potassium in urine was estimated by this method after ashing.

doses of the same salts, however, administered to two additional normal persons, caused the potassium clearance to rise to 37 and 64 c.c., and the concentration of potassium in the serum to 19 to 33 mg. per 100 c.c., but at the same time caused a fall in both the inulin and the urea clearance [11] to less than the normal levels. The minimal values for inulin were 71 and 77 c.c. and for urea 50 and 47 c.c. in these two subjects (table 2). Therefore, in

TABLE II

Renal Clearances: Large Single Dose of Potassium Salt with Toxic (?) Action

Subject (normal person) and surface area, sq. m.	Dose, gm.		Experimental period, minutes	Urine minute volume, c.c.	Plasma and serum clearances*			
	Potassium salt	Potassium†			Inulin	Potassium	Urea	Ratio of potassium to inulin
Fl. 1.80	Control		30	13.8	107	7	99	0.07
			30	10.3	119		76	
	17.5 $KHCO_3$	6.8	30	3.6	71	64	50	0.90
			30	3.8	72	50		0.69
Wi. 1.98	Control		30	10.7	143	10	70	0.07
			30	8.7	145	9	65	0.06
	12.5 KCl	6.5	30	9.1	77	37	64	0.48
			35	2.7	80	36	47	0.45

* Calculated as c.c. per 1.73 sq. m. per minute.
† 0.08–0.1 gm. per kilogram of body weight.

two subjects the large dose of potassium disturbed normal renal excretion. The decreased inulin clearance indicates reduced glomerular filtration. The results of all seven studies reveal that a single dose of a potassium salt containing 80 to 100 mg. of potassium per kilogram of body weight may or may not have a toxic action on the kidney. Obviously such a dose is close to the toxic level for the normal kidney.

Considerable evidence has accumulated that the diseased kidney often can excrete potassium salts satisfactorily.[12, 5] This has been particularly true in cases of chronic glomerulonephritis with edema in which these salts have produced a diuretic action.[12] On the other hand, we now know that it is dangerous to give potassium salts in cases of nephritis in which severe renal insufficiency is present. Caution in their use is especially indicated in cases of severe acute renal failure, of severe passive congestion of the kidney [13, 14, 15] and during the terminal phase of uremia.[15]

EFFECT OF POTASSIUM ON SENSORY NERVE ENDINGS

Because of a certain amount of discomfort in the epigastrium after the ingestion of these large doses of potassium salts it seemed expedient to study

the effect of a potassium salt on renal function after intravenous injection. Such an attempt was made on two healthy volunteers. At the onset of the intravenous injection of 1 per cent solution of potassium chloride both subjects complained of severe burning pain extending from the site of injection in the elbow vein up and along the arm vein to the shoulder. The site and type of pain were apparently similar to those experienced after the rapid intravenous injection of 10 per cent solutions of calcium and magnesium chloride. Further attempts in several other veins also were attended by pain in one volunteer, but the second volunteer managed to take slowly, over a period of 91 minutes, 950 c.c. of the 1 per cent solution of potassium chloride without pain. The concentration of potassium in the serum rose from the control value of 18.3 to 22 mg. per 100 c.c. and the clearance to 58 c.c., but the clearances of inulin and urea were normal, 143 and 67 c.c. respectively (subject Ki. [normal person], table 1). Therefore, this injection did not have any demonstrable toxic effects on the function of the kidney but confirmed the findings of others that a too rapid intravenous injection of a solution of potassium salts gives rise to severe pain along the vein into which the injection is made. Pudenz and his co-workers [16] reported that their patient suffering from periodic familial paralysis, during an attack of paralysis, when the concentration of potassium in the serum was decidedly low, was given intravenous injections of a 0.5 to 2.0 per cent solution of potassium chloride, a total of 1.0 gm. in 10 minutes; the patient complained of such severe burning pain along the vein that on one occasion he stated that he would rather remain paralyzed than submit to such an injection.

The localization of this pain along the veins into which the injection was made naturally suggested that sensory nerve endings for pain in these vessels had been stimulated by the potassium solution. Moore and his co-workers [17, 18] showed experimentally in the cat that intra-arterial injections of potassium salts stimulate the nerve endings for pain in these arteries. Moore also observed, however, that intravenous injections in these animals had no such effect. The investigations of Häbler and Hummel [19] in 1928 revealed that in human subjects intracutaneous injection of isotonic solutions of potassium salts always caused pain within 20 seconds whereas isotonic solutions of similar sodium salts did not cause pain. These facts with regard to the possible stimulation of sensory nerve endings for pain in different tissues by potassium salts offered us a possible explanation of a certain untoward symptom described by Arden [20] after the ingestion by mouth of 15.0 gm. of potassium chloride or potassium bicarbonate. Arden described the development of paresthesia in the hands and feet some 40 minutes after the salt had been taken and its subsequent persistence for three to four hours. Could this paresthesia in the hands and feet be related to an increase in the concentration of potassium in the serum, which in turn stimulated peripheral nerve endings?

In one of our observations the volunteer ingested 12.5 gm. of potassium chloride and while we were studying his potassium and inulin clearances he

complained of paresthesia in his hands and feet. This subject was one of the two volunteers, mentioned already, in whom low inulin and urea clearances developed (subject Wi. [normal person], tables 2 and 3, figure 1). This lat-

TABLE III

Serum Potassium and Paresthesia of Hands and Feet:* Large Single Dose of Potassium Salt; Subject Wi. (Normal Person)

Dose, gm.		Serum potassium, mg. in 100 c.c.	Inulin clearance‡	Paresthesia of hands and feet, grade
Potassium salt	Potassium†			
12.5 KCl	6.5	33.2	77	3

* Two to three hours after ingestion of salt.
† 0.08 gm. per kilogram of body weight.
‡ Calculated as c.c. per 1.73 sq. m. per minute.

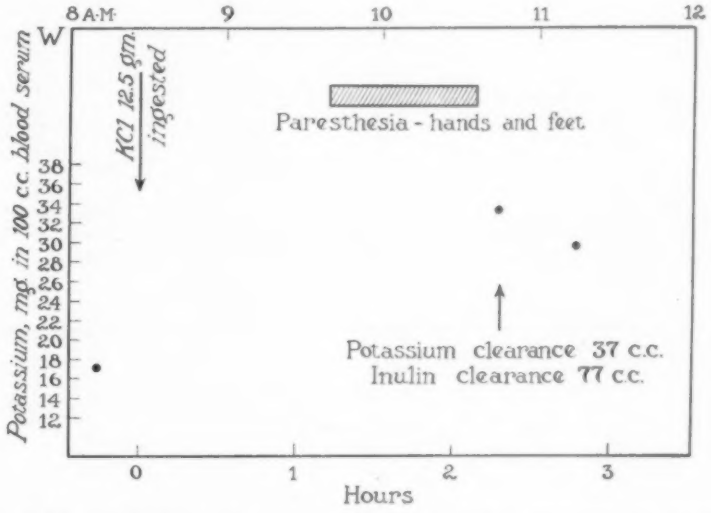

FIG. 1. Subject Wi. (normal person; tables 2 and 3). Concomitant development of paresthesia in hands and feet with a rise in concentration of potassium to 33.2 mg. per 100 c.c. of serum and a reduction of inulin clearance to 77 c.c.

ter finding suggested a possible toxic effect on the kidney while the presence of paresthesia suggested a toxic effect on the sensory nerve endings in the peripheral tissues of the hands and feet. It was noted also that at the time the clearances were estimated and the paresthesia was felt, the concentration of potassium in the serum had increased to 33.2 mg. per 100 c.c. In a similar study of another volunteer we have since observed the development of paresthesia in the hands and feet accompanied by a concentration of potassium in the serum of 32.8 mg. per 100 c.c. (subject Ke. [normal person], figure 2). In a third study, a patient suffering from diffuse cardiovascular disease and hypertension consented to take the same dose of potassium

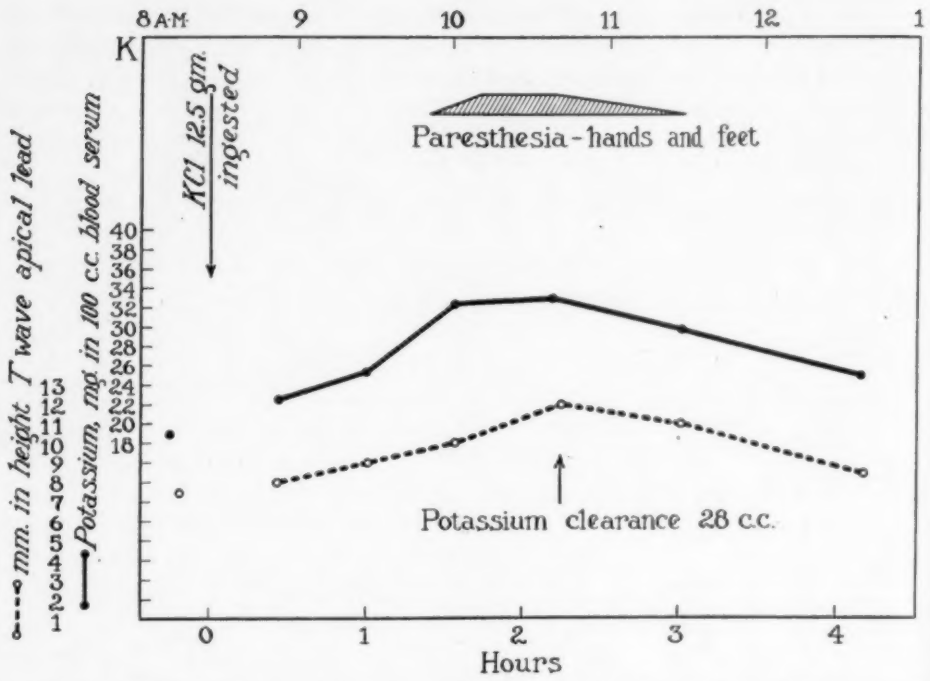

FIG. 2. Subject Ke. (normal person; tables 1 and 4). Concomitant development of paresthesia in hands and feet with a rise in concentration of potassium to 32.8 mg. per 100 c.c. of serum and a rise of 4.5 mm. in the T-wave of the electrocardiogram.

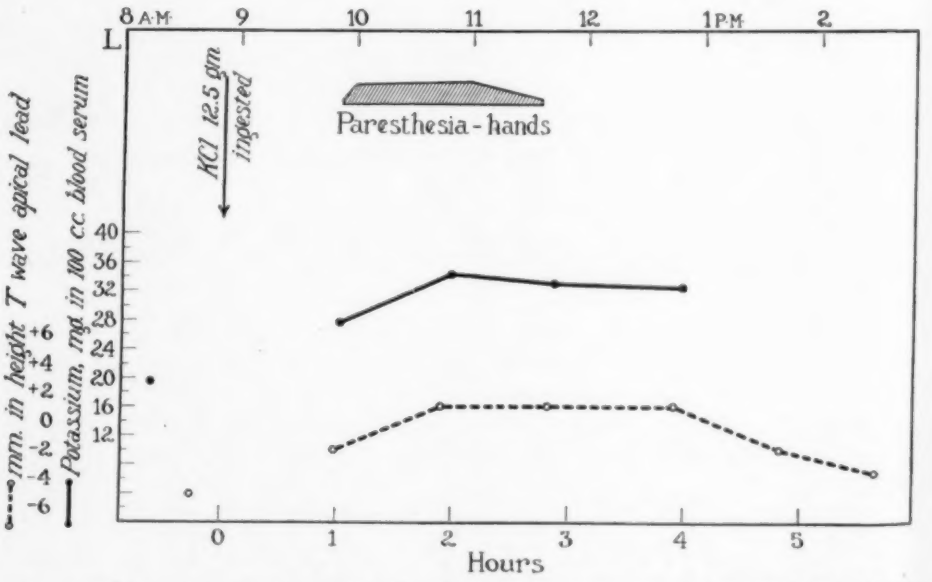

FIG. 3. Subject La. (patient; table 4). Simultaneous occurrence of paresthesia in hands with a rise in concentration of potassium to 34.2 mg. per 100 c.c. of serum and a rise of 6.0 mm. in the T-wave of the electrocardiogram. Note also slow fall of both serum potassium and T-wave.

chloride. Paresthesia developed in his hands but not in his feet when the concentration of potassium rose to 34.2 mg. per 100 c.c. of serum (subject La. [patient], figure 3). On the other hand, a normal volunteer ingested the same amount of potassium chloride but paresthesia did not develop nor did the concentration of potassium rise to more than 26.3 mg. per 100 c.c. of serum. However, he excreted potassium rapidly in the urine, the clearance amounting to 95 c.c. (subject Bu. [normal person], figure 4).* Norn [21] in 1929 re-

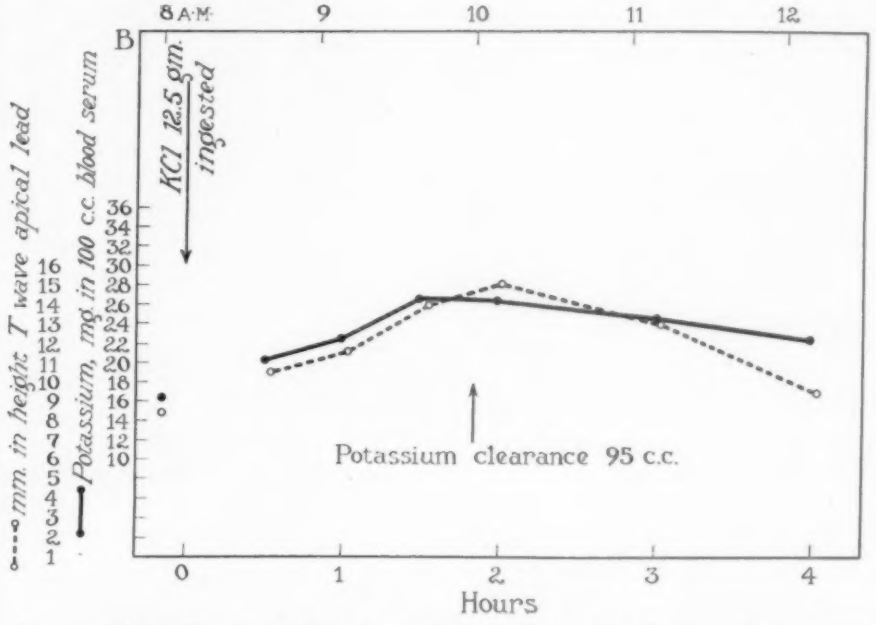

FIG. 4. Subject Bu. (normal person; tables 1 and 4). Simultaneous occurrence of a rise in concentration of potassium to 26.3 mg. per 100 c.c. of serum, a rise of 6.5 mm. in the T-wave of the electrocardiogram and a potassium clearance of 95 c.c.

ported a similar experience to subject Bu. in which paresthesia did not occur. This type of study suggests that there is a close relation between a rapid rise in the concentration of potassium from normal values to 30 mg. per 100 c.c. of serum, and development of peripheral paresthesia.

EFFECT OF POTASSIUM ON THE HEART

Blake, in 1839, and subsequent investigators have suggested that death which followed a rapid intravenous injection of a potassium salt into an animal was due to the sudden cessation of the movements of the heart. Potassium appears to have a dual toxic action on the heart, affecting both the conduction system and the muscle of the heart. Winkler, Hoff and Smith [22]

* This subject's intake of water and output of urine were high in both this and a previous study (table 1). The large intake of water may have played an important rôle in the resulting high potassium clearances; however, in other persons a large volume of urine was accompanied by a much lower potassium clearance.

have demonstrated in their recent experiments the progressive changes that develop in a series of electrocardiograms taken as the toxic action on the animal's heart increases. Similar changes have also been demonstrated in the cat by Chamberlain, Scudder and Zwemer.[22a] Their results confirm the earlier observations of Wiggers [23] in dogs that potassium salts cause a rise in the T-wave of the electrocardiogram early and before auricular or ventricular fibrillation sets in. McLean, Bay and Hastings [24] perfused isolated hearts of rabbits with a fluid containing various concentrations of potassium chloride and demonstrated that increasing the concentration of potassium to 35.3 mg. per 100 c.c. caused a marked rise in the T-wave whereas decreasing it to 11.8 mg. per 100 c.c. had the reverse effect.

There is increasing evidence that similar changes in the T-wave of the electrocardiogram can occur in man. For example, after a normal person has ingested a large dose of a potassium salt a rise in the T-wave can be demonstrated. There are also patients who have certain clinical conditions in which the concentration of potassium in the serum may be increased or decreased abnormally and who show a corresponding rise or fall in the T-wave. Thomson [25] in 1939 demonstrated in examination of a patient who had Addison's disease that a high concentration of potassium in the serum was associated with an increased T-wave in the electrocardiogram. He subsequently showed a similar relation in patients who had cardiac disease and who were ingesting considerable amounts of potassium salts.[26]

In order to follow Thomson's studies further, two normal subjects and a patient who had diffuse cardiovascular disease and hypertension [27] consented to take 12.5 gm. potassium chloride, in a single dose. It is of interest that an electrocardiographic tracing of this patient taken during a control period showed inversion of the T-waves in Leads I and IV. Before and at periodic intervals after the ingestion of the salt, electrocardiographic tracings of the three volunteers were taken and estimations of the concentration of

TABLE IV

Serum Potassium and T-Wave in Electrocardiogram:* Large Single Dose of Potassium Salt

Subject (normal person or patient)	Dose, gm.		Serum potassium, mg. in 100 c.c.	Electrocardiogram, rise in T-wave, mm.‡
	Potassium salt	Potassium†		
Ke.	12.5 KCl	6.5	32.8	4.5
La.§	12.5 KCl	6.5	34.2	6.0
Bu.	12.5 KCl	6.5	26.3	6.5

* Two to three hours after ingestion of potassium salt.
† 0.069 to 0.104 gm. per kilogram of body weight.
‡ T-wave in apical lead.
§ Patient had diffuse cardiovascular disease with hypertension.

potassium in the serum were made.* Both the concentration of potassium in the serum and the T-waves in the electrocardiograms showed in all three studies a steady rise until they reached a maximum in approximately two hours (table 4, figures 2, 3, 4, 5 and 6). In the two normal volunteers

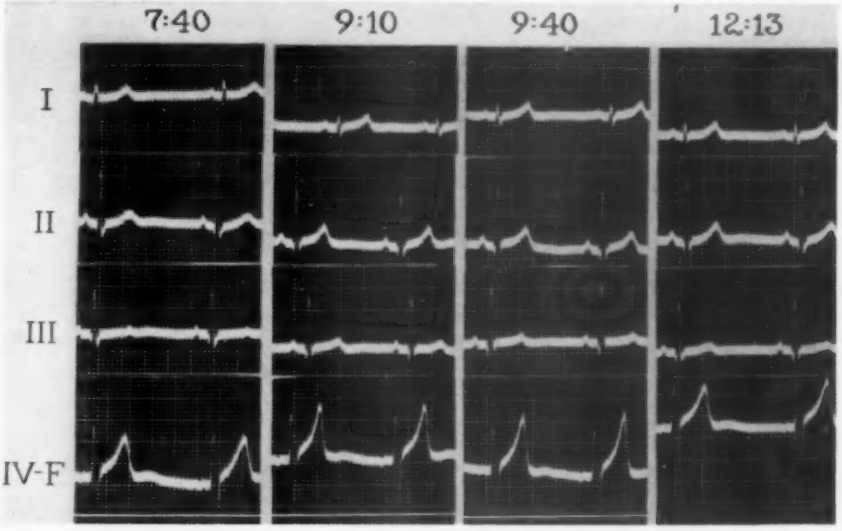

FIG. 5. Subject Bu. (normal person; tables 1 and 4). Changes in the T-wave of the electrocardiogram of a normal person after ingestion of 12.5 gm. potassium chloride at 8:08 a.m.

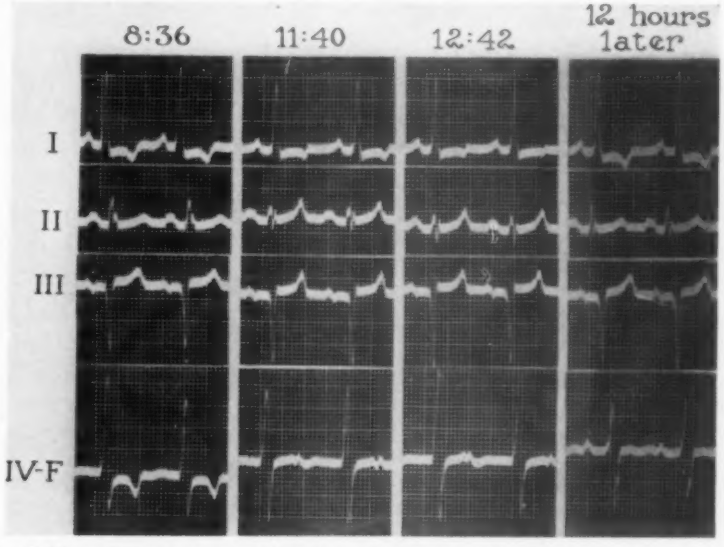

FIG. 6. Subject La. (patient; table 4). Changes in the T-wave of the electrocardiogram of a patient suffering from diffuse cardiovascular disease and hypertension after ingestion of 12.5 gm. potassium chloride at 8:49 a.m.

*The pulse rate was estimated periodically and no marked changes from the normal control rate were observed. Blood pressure readings were not taken during these studies.

there was a gradual decline in the serum potassium and in the T-waves until control levels were approached in four to six hours. However, in the patient who had vascular disease (subject La.) the decline in concentration of potassium in the serum was much slower and even after 12 hours the T-waves had not receded to the control level (figures 3 and 6). It also should be pointed out that in the normal subject Bu. the T-waves rose the highest but the rise in serum potassium was the least (table 4, figure 4). This observation is in agreement with Thomson's findings in patients, that usually the increase in the T-wave was associated with a rise in the concentration of potassium in the serum, but this relationship varied and was not a constant one.

Janota and Weber [28] in 1928 obtained an electrocardiogram in examination of a patient suffering from familial periodic paralysis during a paralytic episode and observed a distinct lowering of the T-wave. With recovery from the paralysis the electrocardiogram became normal. A similar finding was reported later by Zabriskie and Frantz.[29] Several investigators beginning with Aitken, Allott, Castleden and Walker [30] in 1937 have made the interesting observation that during the paralytic attack in such a patient the concentration of potassium in the serum is markedly reduced and that with recovery it rises to normal. Stoll and Nisnewitz [31] early in 1941 made both an electrocardiographic tracing and a serum potassium estimation during an attack of paralysis in one of these patients. As was to be expected, both the serum potassium and the T-waves were reduced definitely.

Simultaneous Diffuse Effects of Potassium

It is quite clear from the foregoing studies that potassium salts after absorption into the blood stream may exert widespread effects throughout the body. Several simultaneous actions in different organs of subjects Wi., Ke., Bu. (normal persons) and La. (patient) are depicted graphically in figures 1, 2, 3 and 4. In subject Wi. (normal person, figure 1) paresthesia in the hands and feet and reduced renal clearances of inulin and urea occurred at a time when the concentration of potassium in the blood stream had risen to 33.2 mg. per 100 c.c. of serum. Apparently at this high concentration of potassium in the serum, the ability of the kidney to excrete inulin and urea was reduced, and the nerve endings in the skin of the hands and feet were stimulated abnormally. In subject Ke. (normal person, figure 2) in addition to the high concentration of potassium of 32.8 mg. per 100 c.c. of serum and the presence of paresthesia in the hands and feet, there is a distinct rise of 4.5 mm. in the T-wave of the electrocardiogram. In this subject we learn that with a similar high concentration of potassium in the serum, as observed in the previous study, abnormal peripheral sensory disturbances occur at the same time as the T-waves in the heart are altered. In subject La. (patient, figure 3) the results are similar to those in the previous subject Ke. (normal person). It is of interest, however, that the T-waves were abnormally low in the electrocardiogram taken previous to the ingestion of potassium and

that the low T-waves were increased distinctly when the concentration of potassium in the serum became distinctly high.

The application of certain technical procedures in these four studies has shown that scattered abnormal functional disturbances sometimes can be correlated with an abnormal symptom, and further that if paresthesia in the hands or feet, or in both, develops after the ingestion of a potassium salt, it is fairly safe to conclude that the concentration of potassium has increased to 30 mg. per 100 c.c. of serum and that T-wave changes can be demonstrated in the electrocardiogram.

Comment

Certain practical considerations emerge from the facts presented in this study. First of all we have learned that protective mechanisms are called into play when too large doses of potassium salts are injected intravenously or ingested by mouth. The stimulation of pain along the vein into which the solution is injected protects the organism from too rapid an entry of potassium into the vascular system and tissue spaces. Likewise after the ingestion and absorption of a considerable dose of potassium the onset of paresthesia in the hands and feet should warn us that the concentration of potassium in the serum has risen quickly to a level which may cause diffuse toxic effects. In a similar manner T-wave changes in the electrocardiogram may be a danger signal, although from present knowledge it is quite clear that their presence alone does not indicate significant dysfunction of the heart. Another practical point is that there are definite indications that in both severe adrenal and renal insufficiency the tissues have a reduced tolerance for potassium salts. This may also apply to patients who have diabetes mellitus.[4] This fact seems true both after experimental adrenalectomy [32, 33] and in patients who have Addison's disease.[34] The problem is not so clear with regard to renal insufficiency. In some abnormal renal states there is greater intolerance than in others to potassium salts. The closer the renal insufficiency is to total loss of renal function in either experimental or clinical conditions,[35, 36, 37, 38] the more likely it seems that there will be intolerance to potassium. However, in moderate renal insufficiency patients often tolerate it well. From these practical considerations one finally concludes that there is considerable individual variation as to what constitutes a toxic dose of a potassium salt, that potassium salts can be given safely in considerable doses in a variety of disease conditions, and that the method of administering moderate repeated doses is safer than giving a large single one.

The fundamental action of potassium salts is related intimately to cellular function * in various tissues. This applies to muscular activity whether in voluntary muscle or the myocardium. Numerous investigators so far have failed to explain adequately the mechanism of potassium in muscular physiology. Some have thought that it was associated intimately with reactions in

* The term "cellular function" refers to both the membrane enclosing the cell and the intracellular protoplasm.

the myoneural junctions, others that its rôle was linked closely with action of hormones such as epinephrine, insulin and cortin within the muscle cell.[39] The beneficial action of potassium salts in familial periodic paralysis and in myasthenia gravis suggests a neuromuscular effect.

A discussion of the diuretic action of potassium salts is of some theoretical interest. Normally after 12 hours of fasting the renal clearance of potassium is remarkably small when compared with that of inulin;[9, 10, 5] the potassium-inulin clearance ratio averages 0.10. This ratio would seem to indicate that a large percentage of the potassium filtered by the glomeruli is reabsorbed by the tubules. With large doses of potassium salts the potassium-inulin clearance ratio rises; in six of our studies on normal persons, the ratio rose to from 0.31 to 0.77. This variable increase in potassium clearance occurred when there was only a moderate increase in the concentration of potassium in the serum, actually from 22 to 28 mg. per 100 c.c. This rise in concentration of potassium in the serum presumably also occurred in the glomerular ultrafiltrate. If from these data one computes the possible reabsorption and excretion of potassium by the tubules, it will be seen that when the potassium-inulin clearance ratio is between 0.31 and 0.45 the absolute amount of potassium reabsorbed is always greater than that excreted. In the one case in which the potassium-inulin ratio reached 0.77, the amount excreted exceeded greatly the amount reabsorbed. The implication of these calculations would seem to be that increased excretion of potassium by the kidney is not always due simply to a rejection of potassium by the tubular cells but is the result of a variable alteration in the balance between reabsorption and excretion in these cells. The diuretic action of potassium salts would appear, therefore, to be the result of a temporary change in the cellular function of the cells of the renal tubules.

The results reported in this paper reveal that the effects of potassium are widespread throughout the body and are in all probability dependent on altered cellular activity. Further knowledge regarding the potassium problem is dependent on the continuance of similar studies as well as on an increased understanding of fundamental cellular physiology.

Summary

A considerable amount of several potassium salts may be ingested by the normal person without demonstrable toxic effects. Similar doses may be given with safety to patients suffering from various diseases, but their use is specifically contraindicated in cases of severe renal and adrenal insufficiency. An important symptom, indicative of toxic action, is the development of paresthesia in the hands and feet. It is accompanied by a rapid rise in the concentration of potassium in blood serum to approximately 30 mg. per 100 c.c. The diffuse action of potassium is revealed by the simultaneous production of effects on the functions of the heart, kidney and peripheral nerve endings.

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TREATMENT OF DIABETES MELLITUS WITH PROTAMINE INSULIN: IS A PERSISTENT GLYCOSURIA HARMFUL? A METABOLIC STUDY OF A SEVERE CASE *

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TWO years ago, we presented our criteria for the satisfactory treatment of diabetes mellitus with protamine insulin. Briefly, we preferred (*a*) one injection a day, and (*b*) we were guided by the patient's weight, (*c*) his freedom from symptoms, (*d*) his freedom from ketonuria, and (*e*) the absence of insulin reactions. The experimental and clinical evidence upon which this treatment was based has been published in detail elsewhere.[1] It was our experience that the most reliable protection the patient had from the hypoglycemic syndrome was a glycosuria. We, therefore, included among our criteria the desirability of a glycosuria.

Our attitude toward glycosuria has been subject to sharp criticism. Joslin [2] and his associates cast some doubt upon our observations, stating that glycosuria of 5 per cent or more and freedom from symptoms was not a reasonable compatibility. Even though we were certain of our records, emphatic criticism from such an authoritative and respected source led us to a review of our data and further experimental work. It is the purpose of this communication to present the results of this study.

From a diabetic population of nearly 2000 we selected one of the most severe and practically uncontrollable diabetics, if a normal blood sugar and freedom from sugar in the urine are considered the ideal. This choice was deliberate, as it was our purpose to demonstrate convincingly that even a severe case can be managed by our standards. We freely admit that it is hazardous to generalize about diabetic therapy; yet we are convinced that if a diabetic of his degree of severity can carry on satisfactorily without complications in spite of his glycosuria, the treatment of the milder and moderately severe patients will hardly offer any difficulties or hazards if our criteria are employed. The patient whose history will be presented in detail is of particular interest, because he has been treated by two methods; (1) in which the aim has been to maintain his urine free from sugar and the blood sugar approaching the normal level using three to four daily doses of insulin and, (2) guided by our criteria in which only one dose of protamine insulin a day was used and the glycosuria was disregarded. Furthermore, between the two periods of hospital observation he was under supervision in the out-

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patient department for three years, during which period he revealed a 4 plus glycosuria most of the time he visited the Clinic. The two hospital periods are not ideally comparable, because on his first admission he was on the general wards. Although the observations and laboratory data are not as detailed and as carefully supervised as they were over the second period of study on the Metabolism Ward of the Russell Sage Institute of Pathology, nevertheless the available data are accurate and reliable.

Case Report

The patient is a 40-year-old male. His family history did not reveal any diabetes. He had never been robust. In childhood he had scarlet fever, following which he was said to have had acute glomerular nephritis. As an adult he had sinusitis and alveolar abscesses. From three years prior to the onset of his diabetes, he had drunk heavily of liquor at irregular intervals. His usual weight has been 58.5 kg. (130 lbs.).

In 1928 he developed the classical symptoms of diabetes, for which he was hospitalized. He responded to the therapy employed and on discharge was receiving 45 units of soluble insulin and a moderate carbohydrate diet. During the hospital period he acquired considerable knowledge about diet, insulin and diabetic management. For three years he was somewhat faithful to instructions but then lapsed into gross carelessness. He had little medical supervision for the following six years from 1931 to 1937. During this period he ate as he pleased, consumed quantities of beer, took insulin irregularly and in varying quantities, at times up to 100 units a day. As a result of this haphazard régime he had three episodes of ketosis, requiring hospital care, and while not under supervision in the hospital he experienced frequent and numerous insulin reactions characterized by convulsions and coma. Many of these occurred at night and were quite alarming. Because of the frequency and severity of these reactions he was admitted to the New York Hospital for study.

Period 1. General Medical Ward. On admission April 17, 1937, the patient was in mild ketosis, which was difficult to eliminate. Since he had a 3 plus glycosuria with this ketosis, 25 units of regular insulin were administered and this was followed by a profound insulin reaction. After proper therapy for this condition, attempts to treat his diabetes with the idea of reducing the blood sugar to normal levels resulted in severe insulin reactions. After three days of careful vigilance and intensive insulin therapy his urine became sugar free, and he was placed on a diet of P 70, F 60, C 300. From that time the medical staff made every effort to control his diabetes by the usually accepted laboratory criteria, that is normal blood sugar and absence of glycosuria. To do this, numerous combinations of insulin, regular and protamine, were tried, but without success. The glycosuria was present at irregular intervals and quite heavy. He also showed acetone bodies on 21 of the 42 hospital days. His blood sugar (fasting) ranged from 40 to 428 mg. Even though a constant régime was attempted without any changes the patient would have insulin reactions on certain days. There were no evident complications which could explain this difficulty in regulation. The management of his pyorrhea alveolaris and dental caries had no effect. There were no other evidences of infection, and a roentgenogram of his chest revealed no pulmonary disease. The peripheral vessels were described as "slightly sclerotic," and soft tissue roentgen-rays of the legs showed a moderate arteriosclerosis with beginning calcific changes, particularly about the ankles. At the end of a 42-day period on the General Ward the patient was receiving 85 units of insulin per day (35–10–30–10 midnight), and the diet mentioned above. The results were never considered satisfactory as at no time could one maintain his urine sugar free and his blood sugar at normal levels without severe reactions. Furthermore, an attempt to reduce the insulin resulted in glycosuria and ketonuria. The patient left the hospital

for financial reasons. His greatest weight during this period was 66 kg. (145 lbs.), his lowest (that at the time of discharge) was 63 kg. (140 lbs.).

Period 2. Out-Patient Department. The patient was then followed in the Out-Patient Department for nearly 3½ years, where he was seen a total of 44 times or slightly more often than once a month. Efforts to reduce the hyperglycemia and the glycosuria were continued, and more than 30 different combinations of regular and protamine insulin were tried. Such changes often were accompanied by the occurrence of mild ketosis on the one hand, and much more frequently, to the despair of the patient, severe insulin reactions on the other. When he reported to the Clinic the 24-hour specimen usually revealed a 4 plus glycosuria. The patient was almost entirely free from the usual symptoms of diabetes, but during 2½ years of this, his weight had fallen about 8 kilos. His diet was never weighed and an estimation of his diet at each visit was usually below the prescription. We appreciate that this estimate is not precise, but nevertheless it gave us an idea that he was not eating as much as he should have. It was estimated that his diet averaged about P 65, F 70, C 180 to 200. In spite of mild insulin reactions the patient led essentially a normal life. He appeared to all observers capable of gainful occupation, although a small income made this unnecessary. He lived alone in a small apartment, ate his meals in restaurants, and was in general frank and coöperative with us. He occasionally indulged in alcoholic bouts, resulting in irregular eating periods and insulin reactions. He had occasional colds but no other serious infection, and no evidence of circulatory insufficiency in the extremities. Since numerous doses of insulin were not productive of the ideal results demanded by some workers in the field of diabetes and since the multiple injections caused him considerable inconvenience, as well as undesirable reactions, we treated him by means of one dose of insulin daily, using the criteria we mentioned above. He was encouraged to eat his total diet, P 70, F 70, C 300. This was covered by 50 units of protamine insulin given in the morning, and he was also advised to have a glass of milk and three crackers at bedtime. At the end of 10 months on this régime of one daily dose of protamine insulin, although he never ate as much as was advised, although he still took alcohol occasionally, and although he always revealed a 4 plus glycosuria in the 24-hour specimen, he had maintained his weight, had no ketosis, had complete freedom from symptoms of diabetes, and only most infrequently mild insulin reactions. There was no doubt in the patient's mind nor in ours that the latter régime suited him best. We were interested at this point to obtain some quantitative data in connection with this treatment, and therefore suggested that he enter the Metabolism Ward of the Russell Sage Institute of Pathology for further study.

Period 3. Metabolism Ward of the Russell Sage Institute of Pathology. On admission October 19, 1940, the physical examination revealed little contributory. He had no complaints, and the detailed laboratory data are in the tables below. During his period of stay the following laboratory determinations were made. The urea clearance tests were 83 per cent and 105 per cent of the normal. Blood cholesterol taken at weekly periods varied from 212 mg. per cent to 282 mg. per cent, the free cholesterol being 41 per cent of the total. The basal metabolic rate varied from —1 per cent to —9 per cent. The hippuric acid test and prothrombin estimation for liver function were within normal limits. Roentgen-ray (soft tissue technic) showed no increase in calcification of leg arteries as compared with films of three years ago, and roentgen-ray of the chest revealed no abnormalities. Throughout the 46 days of the test period the patient was maintained on a diet of P 70, F 80, C 300, a total of 2200 calories. This he consumed quantitatively taking 50 to 60 units of protamine insulin daily. The diet was weighed, prepared, calculated and checked by a trained nursing and dietetic staff. Neither the staff nor the patient's roommate ever observed the patient obtaining extra food. His attitude throughout was one of complete coöperation.

He took mild and fairly regular exercise by walking and pushing wheelchairs in the corridors. As there was a slight ketonuria on admission in some of the fractional specimens the protamine insulin dosage was increased from 50 to 60 units, and although it abolished the ketone bodies from the urine it produced insulin reactions before breakfast. He was finally given 55 units of protamine insulin, and even then there was occasional mild ketonuria in one of the fractional specimens, but no reactions. During his entire hospital stay he was questioned daily by two of us as to the occurrence of symptoms of diabetes. He never complained of thirst, hunger, or weakness. Frequency of urination varied from four to seven times a day, and only on six occasions in seven weeks did the patient void during the night. His total fluid intake varied from 900 to 2800 c.c. a day. His strength, which had never been excellent, remained about the same during the period of study. A careful record was kept of the patient's weight throughout his stay. Every specimen of urine voided was tested for sugar and acetone qualitatively, and then the specimens were pooled and examined quantitatively for total glucose, nitrogen and chlorides excreted in 24 hours. Creatinine determinations were made daily to serve as additional checks on the total output. The stools were not analyzed for nitrogen, but 10 per cent nitrogen loss by this route was assumed. Blood sugar determinations were done at weekly intervals at definite time periods indicated in the second table. Standard methods were used for all laboratory procedures.

Comment

Our clinical and chemical observations reveal certain positive facts. These facts completely and sharply support our previous publications,[1] wherein we categorically stated that even though our patients were excreting large quantities of glucose during a 24-hour period, they "were free from symptoms of diabetes and were in nitrogen equilibrium." We emphasized the fact that during the experimental period the weight loss was not appreciable. This conclusion has been substantiated in the experiment herein presented. The figures in table 1 show that in 46 days the patient lost 0.6 kg. with a glycosuria of 200 gm. + for 5 days, 100 gm. + for 14 days, 50 gm. + for 21 days, and below 50 gm. for 6 days. When this loss of sugar in the urine is translated into the calories lost it is seen in the last 2 columns of the table that the available calories per day varied from 21.3 to 34.5 per kilogram, which is below the Aub-DuBois standards for a man of his age. Of course, these findings are out of line with accepted concepts, yet our chemical analyses have been consistent throughout and the present figures support our former results.

The thought that a patient treated with protamine insulin may reveal a glycosuria and be considered as adequately controlled has been commented on by others,[3] and even such experienced and conservative observers as the Joslin group [4] have disregarded a 24-hour glycosuria up to 10 per cent of the total carbohydrate intake. The controversial point, therefore, is not the glycosuria, but its magnitude. What shall we use as a standard? Shall loss of glucose be 10 per cent, 20 per cent or more of the total carbohydrate intake? It seems to us one cannot make this decision in an arbitrary fashion. To be of value such a standard must be based on either clinical evidence, experimental evidence or both. At present no such evidence is avail-

TABLE I

Experiment started 10/20/40, ended 12/4/40

Patient H. P. Diet P 70 F 80 C 300 Total calories 2200 Total N intake 11.0 gm.

Day of Experiment	Weight in kg.	Urine							N balance	PZI units	Calories lost in 24 hrs.	Available cal. per kg.
		Volume	S.G.	Glucose gm.	Glucose %	Glucose and acetone in fractional specimens *	Chlorides	Total N				
1	59.55	2380	1.027	158	6.6	4 1 4 4 tr 0 tr tr	12.1	7.77	2.23	50	632	24.2
2		2010	1.024	167	8.3	4 4 4 4 4 4 1 0 0 0 0 0	7.2	5.77	4.23	50	668	
3	60.23	2860	1.029	216	7.6	tr 4 4 4 4 4 1 1 1 tr tr 1	13.2	9.00	1.00	50	864	21.3
4		3810	1.026	225	5.9	4 4 4 4 2 0 0 2	17.2	10.50	−0.50	50	900	
5	59.43	3610	1.029	212	5.9	4 4 4 4 0 ft 0 0	19.5	10.82	−0.82	60	848	23
6		2705	1.034	200	7.4	4 4 4 4 4 1 2 2 tr tr	12.5	11.10	−1.10	60	800	
7	59.45	1065	1.029	53	5.0	4 4 4 0 0 0	5.8	3.57	6.43	60	222	33.2
8		1935	1.024	50	2.6	0 0 1 3 4 2 2 0 0 0	12.0		−0.35	60	200	
9	60.15	2285	1.026	84	3.7	2 4 4 4 0 0 0 0	15.1	8.92	1.08	60	336	31
10		2290	1.023	76	3.3	2 2 4 4 0 0 0 0	14.9	8.30	1.70	60	304	

* Upper figure = Glucose; the figure represents the degree, ex 4 = 4 +. Lower figure = Acetone.

TABLE I—*Continued*

Day of Experiment	Weight in kg.	Urine							N balance	PZI units	Calories lost in 24 hrs.	Available cal. per kg.
		Volume	S.G.	Glucose gm.	Glucose %	Glucose and acetone in fractional specimens*	Chlorides	Total N				
11	59.51	1725	1.018	38	2.2	tr 4 4 tr 0 0 0 0	8.5	7.10	2.90	60	132	33.8
12		1365	1.021	18	1.2	tr 0 4 ft 0 0 0 0	5.3	7.82	2.18	60	72	
13	59.99	1490	1.030	57	3.9	4 4 4 tr 0 0 0 0	7.2	8.40	1.60	50	228	33
14		2330	1.028	88	3.8	3 4 4 0 0 0 0 0	8.4	9.35	0.65	50	352	
15		1950	1.034	103	5.3	4 4 4 4 0 0 0 0	8.0	9.40	0.60	50	412	
16	59.69	1990	1.033	100	5.0	4 4 4 1 tr 0 tr 0	9.2	10.35	−0.35	50	400	33
17		1970	1.035	95	4.8	4 4 4 1 tr 0 0 tr	7.5	10.20	−0.20	50	380	
18	59.65	2185	1.034	200	9.2	3 4 3 3 3 vft 0 0 0 0	9.1	9.97	0.03	50	800	23.4
19		1105	1.017	40	3.6	4 4 vft 0 0 vft	7.8	7.67	2.33	50	160	
20	59.67	1860	1.020	56	3.0	4 4 2 0 0 tr	6.3	7.62	2.38	50	224	33
21		1840	1.032	106	5.8	4 4 4 4 0 ft ft 0	8.7	7.97	2.03	50	424	
22	59.06	1460	1.036	107	7.3	4 4 4 tr 0 ft 0 1	7.9	8.53	1.49	50	428	30

TABLE I—*Continued*

Day of Experiment	Weight in kg.	Urine							N balance	PZI units	Calories lost in 24 hrs.	Available cal. per kg.
		Volume	S.G.	Glucose gm.	Glucose %	Glucose and acetone in fractional specimens *	Chlorides	Total N				
23		1110	1.038	62	5.6	4 4 4 ft 0 tr	6.5	8.03	1.97	50	248	
24	59.41	2090	1.030	95	4.6	4 4 4 4 0 0 0 0	11.0	9.40	0.60	50	380	30.7
25		1045	1.034	60	5.7	4 4 4 4 0 0 ft ft	6.3	7.55	2.45	50	240	
26	58.17	2300	1.036	131	5.7	4 4 1 tr 0 1	10.9	9.50	0.50	50	524	28.8
27		1180	1.039	83	7.1	4 4 4 1 0 tr	5.3	7.74	2.26	50	332	
28	59.12	1445	1.030	65	4.5	3 4 4 3 tr 1 1 1	8.0	9.88	0.12	50	260	32.8
29		2050	1.026	87	4.3	4 2 4 4 0 0 tr 0	8.7	8.85	1.15	50	348	
30	59.26	2515	1.033	171	6.8	4 4 4 4 0 0 tr 0	8.9	9.95	0.05	50	684	26.6
31		960	1.032	53	5.6	4 4 4 0 0 ft	3.0	8.57	1.43	55	222	
32		1095	1.020	5	0.5	1 0 0 0 0 0	3.8	9.30	0.70	55	20	
33	59.49	1935	1.027	91	4.7	4 4 4 4 0 0 0 ft	5.0	7.55	2.45	55	364	30.8
34		1995	1.028	91	4.6	3 4 4 4 0 0 0 0	8.2	8.50	1.50	55	351	

TABLE I—*Continued*

Day of Experiment	Weight in kg.	Urine							N balance	PZI units	Calories lost in 24 hrs.	Available cal. per kg.
		Volume	S.G.	Glucose gm.	Glucose %	Glucose and acetone in fractional specimens*	Chlorides	Total N				
35	59.05	2490	1.033	150	6.0	4 3 4 4 0 0 tr 0	11.4	10.08	−0.08	55	600	27
36		2170	1.039	167	7.7	4 4 4 4 0 0 0 ft	6.3	10.63	−0.63	55	668	
37	58.50	1365	1.021	37	2.7	4 4 0 0 0 0	5.9	9.16	0.84	55	128	34.4
38		1190	1.037	53	4.5	3 3 tr 0 0 ft	5.9	8.00	2.00	55	222	
39	58.94	1140	1.023	13	1.2	4 2 0 0 tr 0	6.5	8.62	2.38	55	52	34.5
40		2440	1.034	128	5.2	4 4 4 4 0 0 0 0	10.0	8.57	1.43	55	512	
41	59.22	2690	1.036	173	6.4	4 4 4 4 0 ft ft 0	10.1	11.52	−1.52	55	692	25.5
42		1895	1.039	107	5.7	ft 4 4 4 0 tr 1 0	7.0	9.85	0.15	55	428	
43		1480	1.033	68	4.6	4 4 4 0 0 0	7.5	10.28	−0.28	55	252	
44	58.95	2250	1.030	106	4.7	4 4 4 4 0 0 0 0	9.5	9.42	0.58	55	424	30.1
45		1575	1.033	75	4.8	4 4 4 0 0 0	6.9	7.95	2.05	55	300	
46	58.96	1520	1.032	70	4.7	4 4 4 0 0 0 0 ft	7.5	9.40	0.60	55	280	32.05

able. No one is in a position to state authoritatively whether a glycosuria of 5, 10 or 50 per cent of the total carbohydrate intake is the ideal. We can say, however, from experimental and clinical observation that patients treated with protamine insulin may excrete large quantities of glucose over the periods we have observed and yet reveal no deleterious effects. Furthermore, we are convinced that it is dangerous to attempt too fine a regulation because the excretion of sugar is so irregular and unpredictable that reactions may ensue. Even though the diet, environment, physical and probably mental state of our patient were as constant as experimental conditions permitted, yet the glycosuria was most irregular and extremely variable. With 55 units of protamine insulin daily it varied from 55 to 173 gm. in 24 hours. Furthermore, a slight increase in the insulin dosage resulted in reactions. Chiefly because of a mild ketosis when he entered the metabolism ward we increased his insulin dosage from 50 to 60 units. Three days following this change the ketone bodies disappeared but the patient exhibited, in the presence of a glycosuria, insulin reactions quite severe and alarming on two occasions. This, in addition to subsequent symptoms of milder hypoglycemic episodes resulted in the reduction of the insulin to its original quantity of 50 units. When this dosage was resumed the acetone reappeared. It was only found in some of the fractional specimens in small traces, and it did not bear any relationship to the amount of glucose in the specimens in which it was present. Quite often faint traces of acetone were found in the fractional specimens that *were sugar free,* usually the before-breakfast specimen, and at the following voiding the specimen again showed a 4 plus glycosuria but no acetone. When such traces of acetone were found in only a single specimen, the quantity was too small to react chemically on pooling the 24-hour urinary output. In general, the urinary volume and the specific gravity paralleled the glycosuria, but there were many instances in which this relationship could not be demonstrated. During the first six days of admission the volume varied from 2010 c.c. to 3810 c.c. This we attributed not only to the magnitude of the glycosuria, but also to the order that the patient drink fluids freely and often, and to the additional 6 gm. of salt given daily. When the salt capsules were discontinued the urinary volume decreased. The curious fact was that *at no time* did the patient complain of thirst. He had to be "forced" to drink. The excretion of chlorides was not very illuminating except that it followed roughly the urinary output, rising also when salt was given in addition to the salt in the food. On such days the chloride excretion was high. Once each week the blood sugar was determined at definite intervals throughout the day. It is clear from table 2 that the blood sugar varied from week to week even though the experimental conditions with the exception of slight changes in the dosage of insulin were similar. Furthermore, the changes in quantity of insulin appear to have had no constant effect on the height of the blood sugar curve.

It was our purpose at the outset to confine ourselves to facts and avoid speculative considerations. Our reluctance to enter into hypothetical and

TABLE II

Blood Sugar and Cholesterol Content for Patient *

Date	8 a.m.	11 a.m.	4 p.m.	9 p.m.	Cholesterol	Remarks
10/21/40	53	394	300	230	250	50 units protamine insulin
10/28/40	35	172	272	306	212	60 " " "
11/ 4/40	159	312	500	263	243	50 " " "
11/11/40	91	150	166	136	282	50 " " "
11/18/40	68	248	300	365	250	50 " " "
11/25/40	65	208	197	174	250	55 " " "
12/ 2/40	78	300	300	267	253	55 " " "

* The values for the blood are expressed in milligrams per hundred cubic centimeters.

controversial discussions is based on the experience that after speculations are repeated often enough they are accepted as facts. This is particularly true when one's opportunities to test a given hypothesis are limited. Examples of this are the rooted ideas that hyperglycemia causes arteriosclerosis and predisposes the diabetic to infections. Of course, the most ardent protagonists of these hypotheses admit that the evidence for such assumptions is not very conclusive, yet these statements continue to be perpetuated and quoted as established facts. Apropos of these theories, we have been asked what will happen to our patients over a long period of time, say 25 years, if we treat them by our method and disregard the glycosuria. Since our experience is only about four years old we cannot speak authoritatively for longer periods. We were unable to show progressive sclerosis of the leg vessels by roentgenograms, in this severe diabetic, although we recorded a continuous glycosuria for three years. Furthermore, this patient had no more colds than a non-diabetic and his lungs were clear at all times. Our experience has been similar with other patients. Consequently, although we do not know what may happen to such patients over a longer period of time, our experience with shorter periods prompts us to hazard the thought that they will not suffer from unusual complications. We make this statement reservedly, fully realizing that there is a huge hiatus between impressions and factual knowledge.

Criticism may be directed justly at our therapy for not rendering the urine ketone free at all times. We would have been quite discouraged at our inability to achieve this end, if we did not have the patient's record of three years ago. At that time he revealed traces of acetone just as irregularly even though every attempt was made to render the urine sugar free with 85 units of insulin in four divided doses, and when attempts were made to increase the insulin or reduce the food intake, hypoglycemic reactions supervened. We can offer no explanation for our failure other than the severity of his diabetes. Yet at present this patient is much happier than he was then, because he has only occasional mild reactions, he has reduced the number of injections to one a day, and he has been able to reduce the dosage of insulin as well. He reports to the out-patient department at regular intervals and continues to reveal a 4 plus glycosuria, but no acetone, at every visit. These

are 24-hour specimens. We have asked him to examine occasional specimens for acetone which he has reported as negative. Clinically, he is maintaining his weight, has no symptoms of diabetes, and has no fear of reactions, criteria which we have proposed and consider satisfactory when protamine insulin is used in the treatment of diabetes. Our experience with this method of treatment has been most gratifying and we hope that others will try it. The details of the method have been published,[1] and they demonstrate that our system has simplified diabetic therapy both for the physician and, what is more important, for the patient.

Summary and Conclusions

A severe case of diabetes mellitus is presented in which the treatment with multiple injections of insulin, aiming at a normal blood sugar and sugar free urine, failed to produce as good clinical results as a single dose of protamine zinc insulin, with no attempt to abolish hyperglycemia and glycosuria. On the latter régime, weight was maintained, the patient remained in positive nitrogen balance, he was free from symptoms of diabetes, but occasionally suffered from mild insulin reactions. He was maintained on a diet of protein 70 gm., fat 70 gm., carbohydrate 300 gm., with 50 to 60 units of protamine zinc insulin. Under constant experimental conditions, the glycosuria showed enormous and unpredictable variations. Despite the heavy and continuous glycosuria for three years the patient has not developed any more colds or other infections, than the non-diabetic. His renal function shows no impairment, his atherosclerosis no demonstrable increase.

It is not unlikely that the view point toward glycosuria, when using protamine insulin, will have to be reconsidered, and whereas a good many physicians may still prefer a sugar free urine when treating diabetes mellitus, we want to emphasize that we do not disagree with this plan. If our patients are sugar free and still fulfill the criteria which we have outlined, we do not increase their carbohydrate intake so as to make them excrete sugar. However, when we find that it is extremely difficult to maintain the urine sugar free and avoid reactions, unequivocally we prefer the glycosuria, not only because it makes the patient more comfortable, but because our experience to date has convinced us of its harmlessness.

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SUBACUTE BACTERIAL ENDOCARDITIS; AN ANALYSIS OF FIFTY CASES WITH AUTOPSY FINDINGS *

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COBURN,[1] in his study of rheumatic disease, observed that although this disease is found with great frequency among children and in young adolescents on the medical wards, non-hemolytic streptococcus endocarditis has been infrequent in this age group at the Presbyterian Hospital and has been observed only once on these wards in a patient under 10 years old. This is in agreement with the findings of others. Blumer,[2] in studying 317 cases of subacute bacterial endocarditis, found only one under the age of 10 years. At the Great Ormond Street Hospital for Children, Schlessinger [3] found but 10 cases of subacute bacterial endocarditis in reviewing the postmortem records which had been collected over a period of 65 years. These contain 341 cases of rheumatic endocarditis. Rost,[4] in collecting the cases of subacute bacterial endocarditis occurring in children, says that . . . "in Libman's first 149 cases of subacute bacterial endocarditis, only one occurred in a child under 10 years of age. Observations on children under 14 years of age are scarce in the literature. One rarely finds this condition mentioned and a review of the postmortems of the past half century lists only 64 cases in children." However, although the common type of bacterial endocarditis associated with rheumatic heart disease is a non-hemolytic streptococcus infection, other types of bacterial endocarditis occur in patients with hearts damaged by the rheumatic process. These have included, among many organisms, the hemolytic staphylococcus, the hemolytic streptococcus, the pneumococcus, *Staphylococcus aureus,*[5] *Staphylococcus albus,*[5, 6, 7] gonococcus,[5] and the influenza bacillus. Bacterial endocarditis caused by the pyocyaneus bacillus has been reported by Lenhartz [8] and Thayer,[5] and by the *Bacillus anthracis,* by Young and Blumer.[9]

Coombs,[10] in 1924, determined the average age at onset of the rheumatic infection in 253 rheumatic children who had come under his care to be 10.2 years.

Congenital imperfections of the valves sometimes form the ground work of these bacterial infections. In 1844 Sir James Paget [11] called attention to the frequency with which bicuspid pulmonary and aortic valves are the seat of subsequent disease. This has been emphasized more recently by Lewis and Grant,[12] who brought forward evidence that congenital lesions of the aortic valves often determine subsequent subacute infective endocarditis. Maude E. Abbott [13] has noted and emphasized the frequency with which

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bacterial endocarditis is superimposed on congenitally defective hearts; 17.6 per cent in 555 cases of significant congenital heart disease.

With these observations in mind the writer has analyzed 50 consecutive postmortem examinations on patients with subacute bacterial endocarditis who have come under his observation.

In subacute bacterial endocarditis we have disease in which the most prominent features are distinctly not cardiac. "An ill-defined malaise, slight anemia, some loss of weight, irregular fever, sweats, erratic pains in the limbs, muscles, back or joints, or fingers, or toes, areas of redness or tenderness developing on the hands or feet—one or more of these in any patient in whom a critical examination of the heart fails to pass it as organically sound, should raise our suspicions and should point to a special examination for definite stigmata of endocardial infection." [7] However, late in the disease the symptoms are mainly embolic in nature and an examination of these symptoms, as complained of on admission in the cases investigated, bespeak their variety. In this series, in the order of their frequency they were: dyspnea, pain, fever, weakness, chills, vomiting, paralysis, anemia, cough, loss of appetite, loss of weight, nausea, palpitation, tarry stools, sore throat, hematuria, hemoptysis, coma, bad teeth, nocturia, convulsions, epistaxis, night sweats, incontinence, jaundice, constipation or diarrhea, and nervousness. These symptoms complained of on admission depended largely on the age of the patient. Those 10 years old or younger complained of the following: loss of appetite, weakness, fever, vomiting, convulsions, chills, loss of weight, throat infection, nervousness, bloody expectoration and cough. There was some variation from these symptoms in the group from 10 to 20 years of age, whose chief complaints were chills, fever, joint or muscular pains, tarry stools, weakness, vomiting, anemia, palpitation, heart pain, nodes and petechial eruption.

The age incidence in these 50 cases was:

Up to 10 years	6
11 to 20 years	3
21 to 30 years	9
31 to 40 years	17
41 to 50 years	10
51 to 60 years	5

Six more cases were seen, but were excluded from this series because of their age and the possibility that their infectious endocarditis was a terminal manifestation rather than the primary cause of death. Their ages were 59, 66, 67 (two), 75, and 78 years.

There were 28 males and 22 females, 45 white and five colored patients.

The age incidence is of interest, for, as previously mentioned, many investigators have found non-hemolytic streptococcus endocarditis infrequently among children and young adolescents, and there is some question how early in life this condition can occur. The following case, not among the 50 in

this series, is mentioned because of the age of the patient, the implications of the case and the pathological possibilities it may engender.

Case 1. The history is as follows: A female baby had been delivered of an American mother, Mrs. McC., white, 40 years of age primigravida. It was a natural delivery. On the second day the baby was unusually quiet; she became lethargic with a slight bluish discoloration to the skin which deepened until death. The Wassermann reaction was negative for the baby and both parents. The autopsy findings showed a well-nourished white female infant. The head was negative; the lungs showed diffuse areas of atelectasis; the heart showed a small nodule two millimeters in diameter on the mitral valve which had the appearance of a vegetation. (Figure 1.) Otherwise the heart was negative, as were the other organs.

FIG. 1. Baby McC., aged two days, a vegetation two millimeters in diameter on the mitral valve.

Microscopic examination showed atelectasis of the lungs; normal myocardium. Section of the vegetation showed focal areas of endothelium in which there was an increase of connective tissue, and an absence of lining endothelial cells. It was regarded as a small focal scar on the mitral valve.

Fetal and infant endocarditis has been reported recently,[14, 15, 16, 17] as well as an endocardial vegetation in an infant one year of age.[18] Abraham [19] reported a case of an infant four days old, presenting somewhat the same symptoms as the above, in whom thickened bicuspid aortic and pulmonary valves and a mural vegetation of the left ventricle were found at postmortem examination. Lawson and Palmer [20] reported three cases occurring in children aged six, eight and 10 years respectively and one case of *Streptococcus viridans* septicemia, without demonstrable valve lesions, in a child aged 12 months. Leech [21] reported *Streptococcus viridans* endocarditis, proved

by autopsy in 15 cases in children, three of whom were under five years of age and one 21 months.

Blood cultures before death were positive in 23 cases, sterile in 10, and were not taken in 17. That this diagnostic procedure was neglected in 34 per cent of patients dying of infectious endocarditis bespeaks the deceiving and misleading symptomatology of the disease, the complaints on admission being such as to divert attention from the primary disease to the complications, as illustrated by the following case.

Case 2. M. B., a white female, aged 30 years, was admitted to the surgical service on September 23, complaining of pain in the left lumbar and the right iliac regions of the abdomen.

The following history was obtained from the patient. Menstrual periods had been regular up to one year before admission, since which time periods of menorrhagia and metrorrhagia had been experienced. Two months before she had been admitted to another hospital for a sharp pain in the left groin radiating to the lack. She was discharged 27 days later improved, the diagnosis being sacroiliac and intervertebral arthritis, a laceration of the perineum, and a lacerated cervix with fixation of the fundus to the left.

The past history was irrelevant. The onset of her menstruation was at 16 years of age; it had always been regular, every 28 days, and of four to five days' duration, the last period occurring 17 days before admission. She had had 10 pregnancies, six of which terminated spontaneously.

Physical examination revealed a white female, subacutely ill and poorly nourished. The teeth were in poor condition. The fauces, pharynx and tonsillar areas were moderately inflamed. The submaxillary glands were enlarged but not tender. The chest was normal. The cardiac apex impulse was one centimeter outside the midclavicular line. There were no murmurs. The abdomen was enlarged; there was spasticity of the muscles and tenderness in both lower quadrants. There was an herpetiform eruption about the lips. The temperature was 101° F., pulse 110, and respirations 22. The blood pressure was 136 mm. Hg systolic and 86 mm. diastolic.

The patient on admission presented the history and physical signs of a chronic pelvic infection.

Roentgen-ray examination showed a sacroiliac arthritis of moderate degree on the left side. There was no evidence of abnormality of the dorsal vertebrae. There was evidence of a productive arthritic process about the left halves of the second and third lumbar vertebrae. Stereoscopic examination of the hips revealed no evidence of abnormality. The femur was normal. Pyelograms also were negative; catheterized urine showed no albumin or red blood cells; there was only an occasional white blood cell from each ureter.

The Wassermann and Kahn reactions were negative. The blood examination on admission showed red blood cells 4,000,000; white blood cells 9,300; polymorphonuclear leukocytes 83 per cent, lymphocytes 16 per cent, large mononuclear leukocytes 1 per cent. The hemoglobin was 70 per cent. Subsequent examination showed a steady drop of red blood cells to 2,750,000, and hemoglobin to 50 per cent, and a rise in white blood cells to 22,000, polymorphonuclear leukocytes to 92 per cent, with lymphocytes 8 per cent.

The patient was more comfortable in a dorsal recumbent position with the knee flexed. The abdominal tenderness became more prominent in the right lower quadrant increasing toward the right lumbar region. Pelvic examination showed no evidence of inflammation. There was a thick dark discharge from the lacerated, eroded and everted cervix, but no masses were felt and no tenderness was elicited. A rectal examination was negative.

Nineteen days after admission a pneumonitis occurred at the left base, with a rise in temperature ranging from 102° F. to 105° F. The pulse was 120 to 140 and the respirations 16 to 32. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. A few days later a similar area of pneumonitis was noted at the right base. Frequent examinations revealed no evidence of cardiac disease not concomitant with the prolonged fever. On the day before death, the thirtieth after admission, two petechiae were observed on the left conjunctiva.

The postmortem examination revealed the body of a young white girl about 30 years of age. There were many hemorrhages in the sclera of the left eye. A midline incision and removal of the sternum revealed the right lung adherent at the base; many small infarcts were present. The left lung showed infarcts with a large thrombus

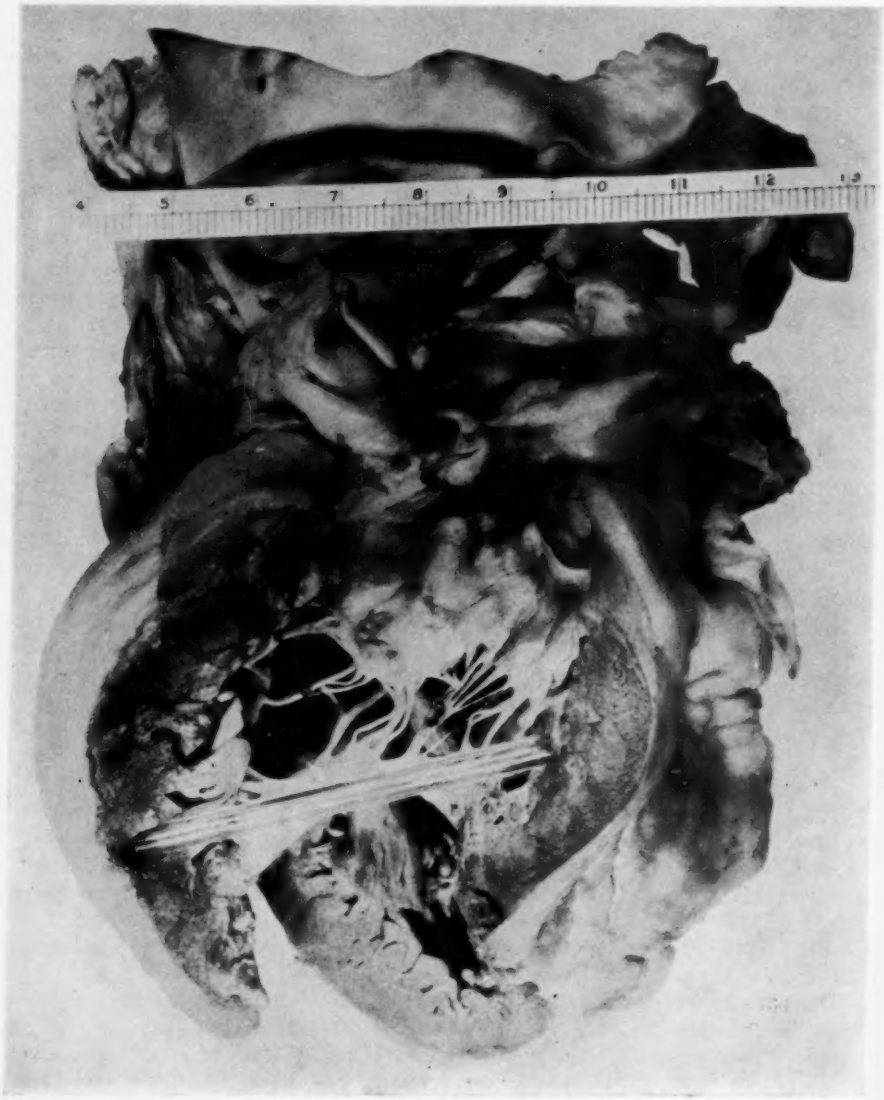

FIG. 2. Numerous verrucae on the mitral valve.

in the lower branch of the pulmonary artery. The heart was small and there were numerous verrucae on the mitral flap; they were red, granular and of bacterial origin. The spleen was twice the normal size with large emboli and showed numerous small infarcts. The left iliac vein contained a thrombus adherent to the wall of the vein and giving complete obstruction.

Microscopical findings were as follows. The lungs showed hemorrhagic infarcts; the heart, thrombotic changes continuous with the endothelial layer. There was a small area containing many polynuclear cells and bacterial colonies. (Figures 3 and 4.) The myocardium showed much fatty degeneration and new connective tissue

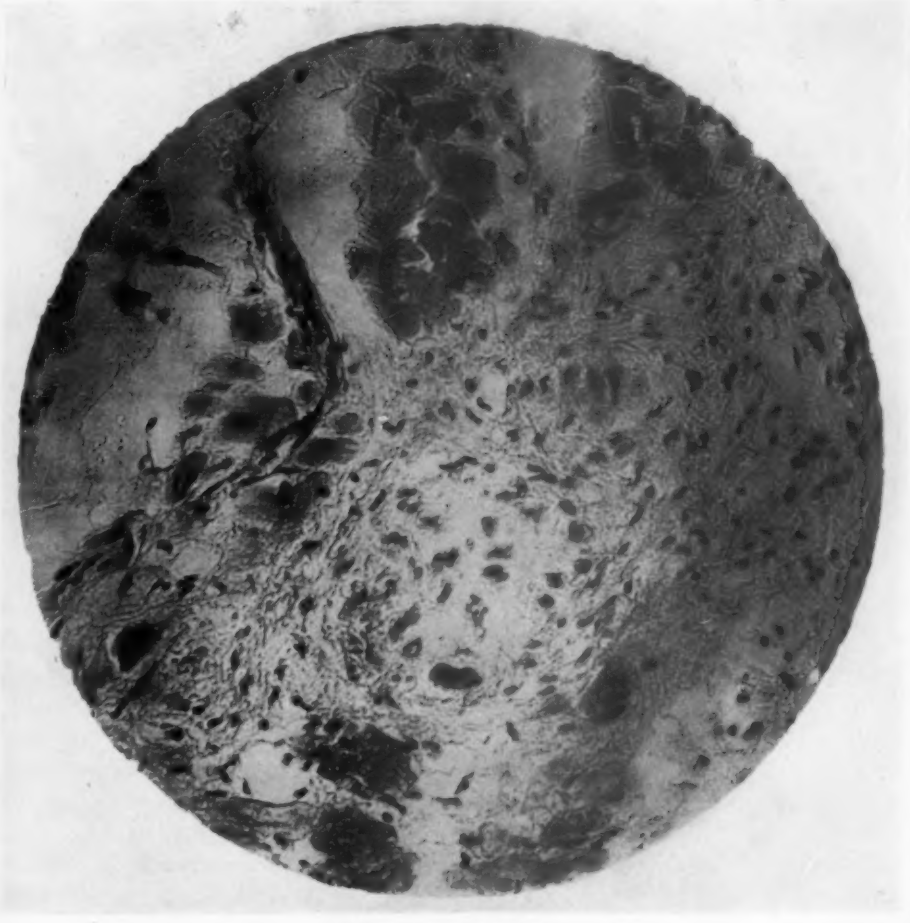

FIG. 3. Aschoff body.

formation. There were also hemorrhages in the myocardium between the fibers. The spleen showed infarction with areas of necrosis and perivascular round cell infiltration. The liver showed focal necrosis. Embolic glomerular nephritis and congestion were present in both kidneys. The adrenal glands showed marked degenerative changes, cloudy swelling and necrosis.

The cause of death was subacute bacterial endocarditis, viridans type, and multiple emboli with infarcts of the kidneys, spleen, lungs and the iliac veins.

This confusing surgical problem proved on postmortem examination to be purely medical. The history emphasized the gynecological aspect, tending to divert attention to the complications and from the cause as is so common in this condition. In retrospect, however, areas of embolic pneumonitis and tender kidneys were the clues overlooked. An early positive blood culture

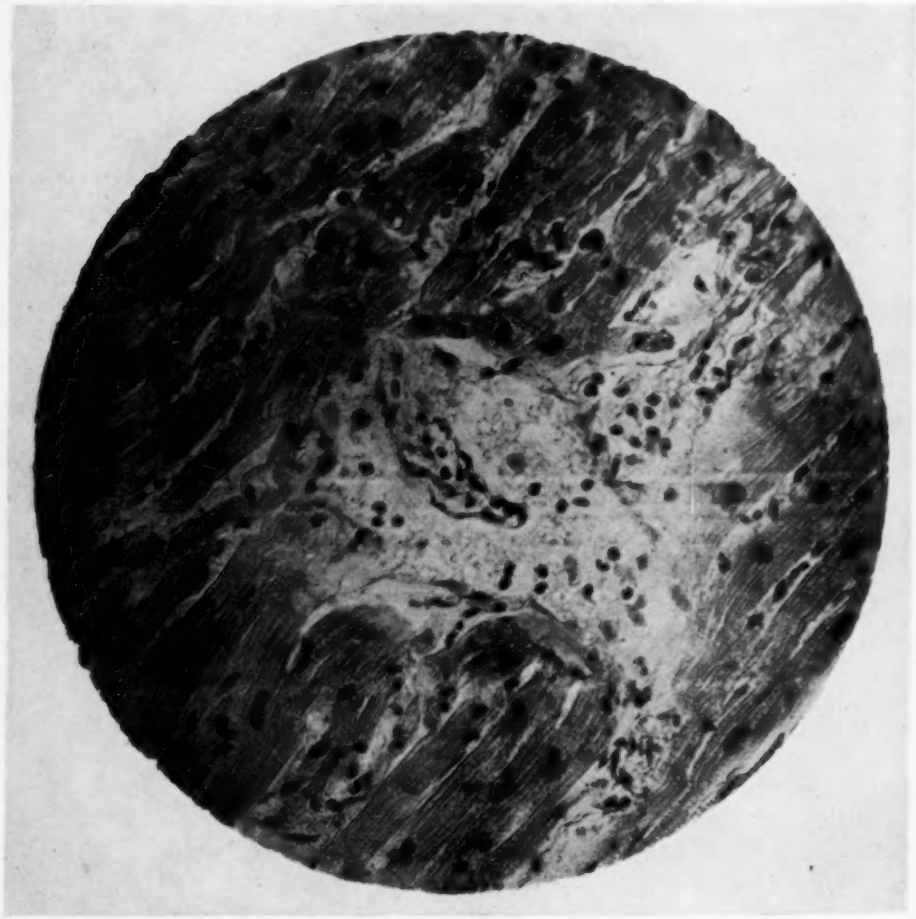

FIG. 4. From the same patient as figure 3. Bracht-Wachter lesion.

will explain what otherwise may develop into a confusing malady. The absence of red blood cells in the urine in this case is unexplained.

Of those patients showing a positive blood culture, the *Streptococcus viridans* was present in 19, and staphylococci were present in four, one of which had a mixed staphylococcus and *Streptococcus viridans,* and one of which showed a culture of a Gram positive bacillus.

The duration of subacute bacterial endocarditis is difficult if not impossible to estimate in the vast majority of cases. What may be taken as the

onset may be an incident in the course of the disease, or the patient may be wholly unaware of the fact that he is the victim of a serious illness until the occurrence of embolic phenomena.

The former type is well illustrated in the following case of a verrucous endocarditis in a child four and one-half years of age.

Case 3. E. U. was admitted to the hospital in convulsions, with fecal and urinary incontinence, tonic and clonic spasms, and vomiting. The child died a few hours after admission.

The history obtained from the parents was irrelevant. They insisted that the child had been in good health up to the morning of admission, when she experienced severe chills, followed by a high temperature and convulsions.

The postmortem examination revealed the body of a well-nourished and well-developed white female child four and one-half years of age. There were numerous small petechial spots distributed over the arms, legs and neck.

The heart was free in the pericardial sac, and normal in size. The epicardium was congested, and on section the myocardium was firm, somewhat edematous and nut-colored. The mural endocardium was clear; there was evidence of mural thrombosis. The mitral valve leaflets showed three areas of vegetation formation on the upper or auricular surface which coalesced to some extent. These vegetations were reddish-brown in color and stood out prominently against the normal appearing valve leaflet.

There was a persistent thymus present weighing 50 grams. This gland was reddish-brown in color, moderately firm, and surrounded by its capsule.

The head showed no abnormalities.

Histological examination: The thymus gland showed hyperplasia. The myocardium showed segmentation and fragmentation; a round cell infiltration was present. The heart valves showed a chronic fibrous endocarditis. There was a more recent exudate on the mitral valve, an increase in fibrous tissue, round cell infiltration, and absence of lining endothelial cells.

The lymph glands showed reticulo-endothelial proliferation.

The above case of a child who died 18 hours after the onset of an unexplained illness and who, hitherto, had been thought to be in good health by an unobserving mother, shows one of the problems in the diagnosis of this condition.

The next case will illustrate the latter instance of failure to discover the true nature of this disease.

Case 4. A. P., a white Italian laborer, aged 39 years, was admitted to the medical service of Kings County Hospital, complaining of pain in his left leg of two days' duration. On the day before admission he worked as usual as a laborer, lifting and carrying bricks, and was not uncomfortable until night, when he experienced a pain in his left lumbar region radiating to his left hip. The pain became progressively worse, preventing sleep and making it impossible for him to stand erect.

The family history was not contributory.

The patient's previous personal history disclosed that he had had a similar attack one year previously, and since then six such seizures, less severe and shorter in duration than the present one.

The physical examination showed a well developed and well nourished male, complaining of acute pain in his left hip. The temperature was 100° F., pulse 90, and respirations 21. The blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. His few remaining teeth were carious. His lungs and heart disclosed nothing ab-

normal. The abdomen showed a moderate spasm of the recti muscles but no tenderness: deep pressure in the left iliac region gave referred pain in the left hip. The reflexes were normal. The left leg was painful on motion. A provisional diagnosis of osteomyelitis of the left hip was made and an orthopedic consultant concurred.

The blood examination showed: white blood cells 7,600; red blood cells 4,350,000; hemoglobin 75 per cent; polymorphonuclear leukocytes 89 per cent, mononuclears 4 per cent, lymphocytes 7 per cent. The blood Wassermann and Kahn reactions were negative; blood culture showed a *Staphylococcus aureus.*

Operation was performed the same day for an osteomyelitis of the left hip, and examination of the scrapings confirmed this opinion.

The subsequent course was unfavorable; the patient presented the signs and symptoms of cerebral irritation and died on the ninth day of hospitalization.

Postmortem examination of the tissues showed an embolic encephalitis; cloudy swelling of the myocardium; emboli, fragmentation, segmentation and a subacute endocarditis of the aortic cusps; and an ulcerative aortitis. The lungs showed chronic passive congestion and anthracosis; the spleen, numerous bacterial emboli and infarcts. There was an infarction of the ilium. On removal of the right kidney there was noted a diffuse hemorrhagic infiltration into the retroperitoneal tissue which extended down the right side into the pelvis proper and encircled the rectum.

In this study of the postmortem cases under consideration there was no case of congenitally deformed heart, and not all showed evidence of previous valve damage, although evidence of old subendocardial infiltration was noted. This is readily understood as myocardial infiltration is a characteristic feature of rheumatic carditis. Of 23 cases coming to postmortem examination, 22 showed characteristic perivascular, Aschoff bodies.[5]

"Subacute bacterial endocarditis never develops in a previously normal heart, but rather in those who have some abnormality of the valves or endocardium, either rheumatic or congenital in origin. In general it may be said that 20 to 25 per cent of all cases suffering from valvular disease succumb to bacterial endocarditis." [22] However, fatal subacute bacterial endocarditis may develop soon after the initial rheumatic invasion, so soon after as to be a continuation of this process. In one child three months elapsed between the primary attack of rheumatism and death from subacute bacterial endocarditis.

The location of the verrucae when found on one valve only was as follows:

Mitral	21
Aortic	10
Pulmonic	1
Tricuspid	1
Mural	2
Epicardial	1 [23]

When more than one valve was involved, they were found in the following combinations:

Mitral, aortic and tricuspid	1
Mitral and tricuspid	2
Mitral and aortic	3
Mitral and mural	4
Aortic and tricuspid	2
Mitral, aortic and mural	1
Aortic and mural	1

Levine expressed the opinion that the vegetations of subacute bacterial endocarditis are usually found on postmortem examination to involve more than one valve, but when they are confined to one valve they are almost as common on the mitral as on the aortic leaflets.[22]

Three hearts showed old healed verrucae with active vegetations also present. Two showed healed vegetations on postmortem examination; one of these, previously reported,[23] showed a healed ectodermal lesion and an active secondary focus in the adventitia of the left renal artery; the other showed healed verrucae on the aortic valves. A brief summary of this latter case may be of interest for it aptly illustrates the observation of Libman [24] regarding patients in the bacteria free stage of the disease. Such patients have overcome the active infection, but have sequelae, such as subacute and chronic glomerular nephritis, progressive anemia, embolism and splenomegaly. They have recovered from the infection of the heart valves but die as a result of the damage that has been inflicted during the active, infective stage of the disease. They invariably succumb to the pathological changes necessary to overcome the active process.

Case 5. F. S., a white boy, nine years of age, was admitted to the medical service of St. Peter's Hospital, complaining of vomiting, weakness and pain over the heart.

The following history was obtained from the patient. The present illness started two weeks before admission, with a "cold," herpes on the lips, and a gradually progressing weakness with loss of appetite and weight. The patient became breathless on exertion and a low grade irregular fever was noticed.

The family history was irrelevant. The patient had had the usual childhood diseases and frequent sore throats.

His temperature on admission was 99.6° F., pulse 110, respirations 24. The blood pressure was 118 mm. Hg systolic and 76 mm. diastolic.

Physical examination revealed a white boy acutely ill, pale and moderately emaciated. The tonsils were inflamed and cryptic. The heart was enlarged to the left. The apex impulse was in the fifth interspace outside the midclavicular line. There was a rough systolic murmur of maximum intensity at the apex, partially replacing the first sound and transmitted to the axilla. A short presystolic murmur was present. There was no thrill palpable. The abdomen was normal.

The diagnosis on admission was rheumatic endocarditis.

Blood examination showed red blood cells 3,425,000, white blood cells 15,700; polymorphonuclear leukocytes 82 per cent, small lymphocytes 10 per cent, large lymphocytes 8 per cent; hemoglobin 70 per cent. The red blood cells showed normal morphology. The urine was turbid, amber in color, with a specific gravity of 1.039. There was no albumin, sugar, pus cells or red cells present. The blood sugar, creatinine and urea nitrogen were within normal limits. Sedimentation time was 20 minutes in the first tube and 15 minutes in the second on admission; it went to 13 minutes and later rose to 29 minutes. Fragility began at .40 per cent sodium chloride and ended at .32 per cent. The blood Wassermann reaction was negative. The first positive staphylococcus blood culture was obtained three weeks after admission. The throat culture showed a preponderance of staphylococci and streptococci; Gram negative diplococci were also present.

On admission and while under observation the only suggestive signs of an infectious endocarditis were an increasing anemia, and petechiae which appeared in both conjunctivae in the early stages of this disease. During the period of hospitaliza-

tion, three and one-half months, the patient had two attacks of an embolic pneumonitis. He received two small transfusions of 250 cubic centimeters each and was discharged with a normal temperature, pulse and respiration.

The diagnosis on discharge was subacute bacterial endocarditis, staphylococcus bacteremia, but owing to the apparent improvement of this patient, the sterile blood culture on discharge, and the absence of embolic phenomena, except the early petechiae, the correctness of this diagnosis was doubted.

This patient was again admitted to St. Peter's Hospital three months later with signs of cardiac decompensation.

The history on this second admission was that he had been enjoying fair health while at home until one month previously, when gradually increasing dyspnea was noticed. He had been allowed up out of bed and even permitted to go down to the street to play, four stories below.

The physical examination at this time showed a cyanotic, orthopneic boy suffering from cardiac decompensation. There were basal râles in both lung fields. The heart was enlarged. The apex impulse was in the fifth intercostal space almost in the anterior axillary line. There was a soft systolic thrill at the apex with a harsh systolic pericardial rub, and a rough to-and-fro pericardial rub at the base. Capillary pulsation and a Corrigan type pulse were present. The liver was not enlarged. The spleen was enlarged. The fingers were clubbed to a marked degree.

During the second admission to the hospital, the physical signs were those of severe cardiac embarrassment owing mainly to an adhesive pericarditis. Pleural and pericardial effusion were present and fluid was withdrawn whenever necessary for the relief of the patient. Examination of this fluid showed it to be bloody and sterile on culture.

Repeated blood cultures were sterile.

The patient died eight months after his second admission with signs of cardiac failure.

Postmortem examination revealed marked biliary pigmentation of the scleral conjunctiva, extreme emaciation of the upper part of the body, edematous lower extremities, and fluid in the abdomen.

The lungs showed a bronchopneumonic area of the right base which appeared to be due to a terminal infarct. There was no embolus in the artery. The left lung was adherent to the pericardium.

The heart on examination showed marked dilatation of the left ventricle. The mitral valves were clear. On the edge of the aortic valves which were sterile on culture there were many old sclerotic verrucae. There were subendothelial markings and a marked adhesive pericarditis.

Libman, in discussing Sir Thomas Horder's paper on this subject at the 85th Annual Meeting of the British Medical Association,[7] was led to believe from observations up to 1917 on a series of 109 cases, that 25 per cent of persons having an infection of the valves of the heart by an anhemolytic streptococcus spontaneously lose their infection and die of the after results. "We have no idea of how often the infection may occur without being clinically observed and complete recovery follow."

In a review of the postmortem findings in patients dying of subacute bacterial endocarditis, the pathology encountered in the heart and pericardium is of primary importance. Coombs [10] found from the Bristol General Hospital postmortem records that among patients dying of rheumatism in the first decade 100 per cent showed pericardial lesions; in the second decade

83.3 per cent; in the third, 41.6 per cent; in the fourth, 23.0 per cent; after the age of forty, 26 per cent, and taking all together 53.0 per cent. A large number of autopsies in patients dying at or before the age of 16 years of

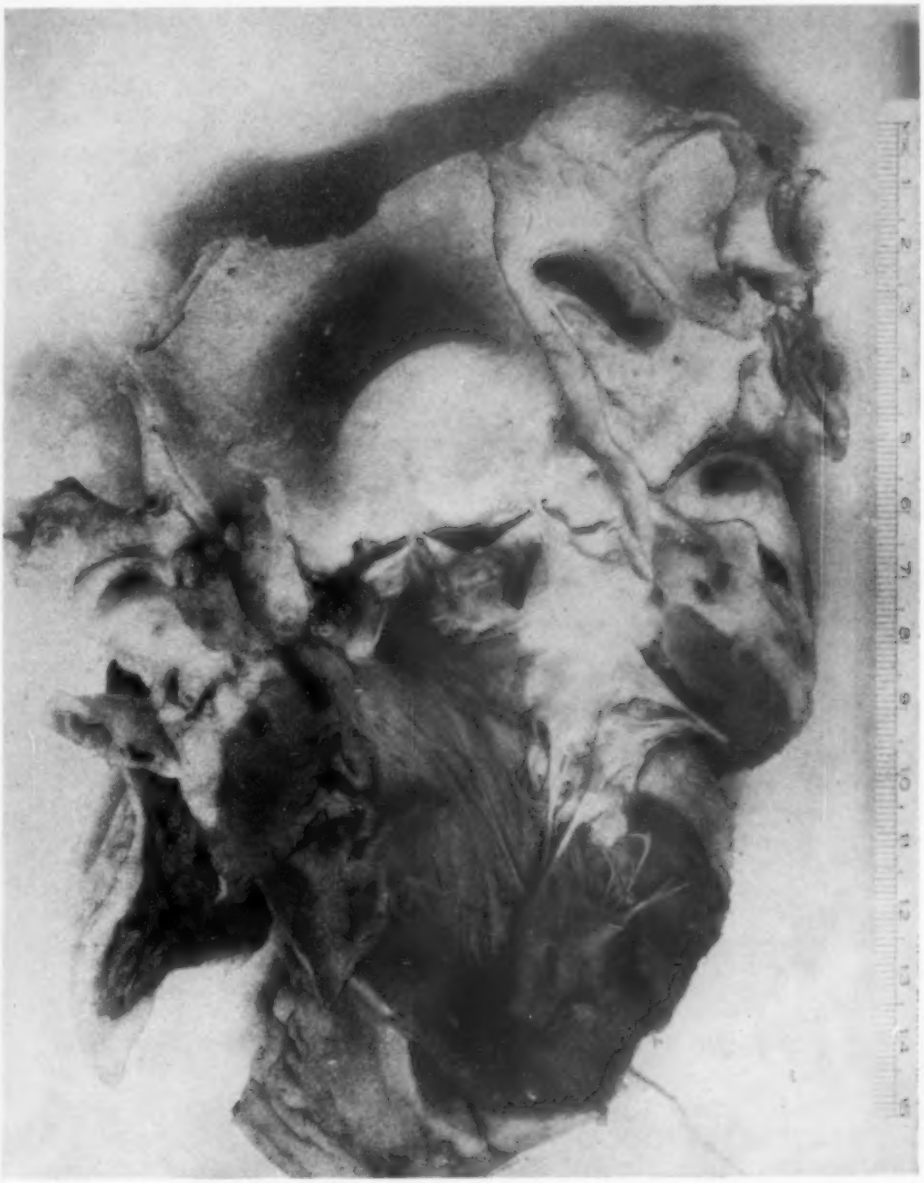

FIG. 5. Subacute endocarditis of the aortic cusps.

rheumatic carditis showed effusions of a measurable quantity in less than 10 per cent, the average volume of the effusion being between four and five ounces. The deduction made by Coombs was that fluid rarely collects in the

pericardium in the rheumatic heart in quantities sufficient to collect for instrumental evacuation. Coombs [25] previously, in speaking of the differences between rheumatic and infectious endocarditis, stated that the difference is very definite, that in subacute bacterial endocarditis the endocardium is much injured, the myocardium slightly and the pericardium not at all. (Figures 6 and 7.) Thayer [5] found pericarditis in two of 25 cases which had come to postmortem, or 8 per cent. Camp and White,[26] in an analysis of 1729 autopsies at the Massachusetts General Hospital, found that pericardial effusion of more than 100 cubic centimeters was present in 126 cases, 7.2 per cent. This stresses the fairly frequent presence of pericardial effusion in small amounts; 94 had less than 250 cubic centimeters. In 80 cases of subacute bacterial endocarditis reported by Clawson and Bell,[27] pericarditis was found in 18, 22.5 per cent. The normal amount of pericardial fluid may vary, but its amount is never large. At autopsies performed a few hours after death, a few cubic centimeters of clear, light yellow serum are usually found in the pericardial sac.[28] Cunningham [29] states that the pericardial sac contains a little fluid.

In my cases reported here the following postmortem findings were noted:

Hydropericardium		18
Pericarditis		13
Fibrous	9	
Adhesive	4	
Myocarditis, chronic fibrous		14
Endocarditis, old rheumatic lesions		29
Chordae tendineae	4	
Mitral	17	
Tricuspid	4	
Aschoff bodies	2	
Bracht-Wachter bodies	6	
Both Aschoff and Bracht-Wachter bodies (case 2)	1	
Pulmonary pathology:		
Pleural effusion	8	
Pleural adhesions	18	
Pneumonia	21	
Broncho	14	
Lobar	7	
Lung collapse	1	
Embolus	2	
Infarcts	8	

Kidney pathology as noted in 33 cases was as follows:

Acute glomerulitis	2
Acute and chronic nephritis	2
Vascular nephritis	1
Degenerative nephritis	1
Infarction	17
Embolic glomerular nephritis	6
Chronic focal glomerulitis	4

The spleen showed infarction in 27 cases. Infarction of the dome of the spleen may cause a pleuritis at the base of the left chest [18]; this may be the first complaint in a patient active and with no previous incapacitation, and be treated as such, without recognition of the serious nature of the disease, of which this is but a symptom.

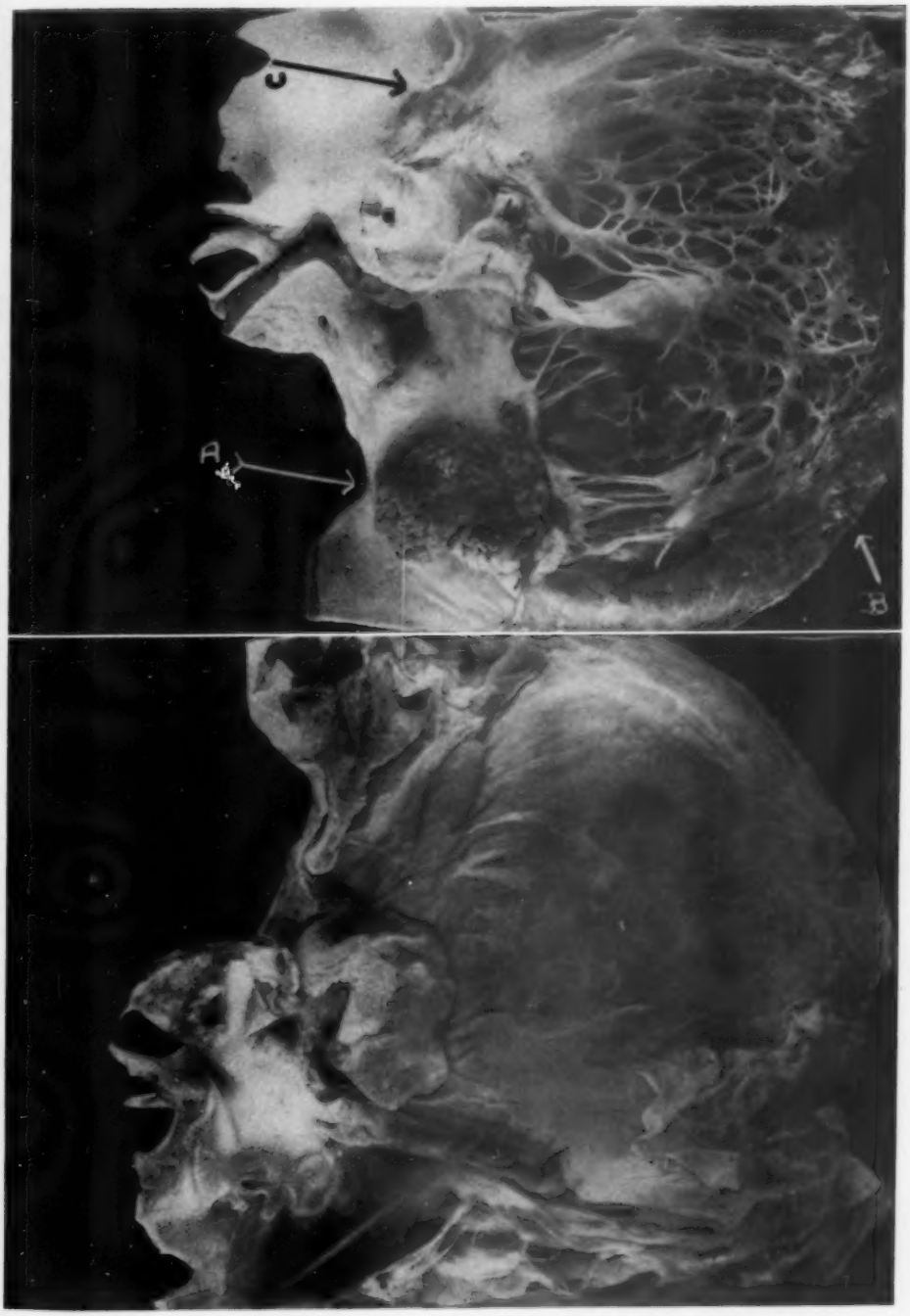

FIG. 6 (above). (*a*) Subacute bacterial endocarditis of the mitral valve, *Streptococcus viridans* infection. (*b*) Secondary intramural focus. (*c*) Old rheumatic beading of the aortic and mitral valves.

FIG. 7 (below). The same patient as in figure 6. Marked adhesive pericarditis.

Thrombus formation was distributed as follows:

Right cerebral artery	1
Pulmonary artery	3
Iliac vein	2
Epicardial vessels	1
Common iliac artery	1
Renal artery	1

It has been stated that enlargement of the spleen is a common and early finding in bacterial endocarditis; this has not been true in my experience with this disease. An enlarged liver, often tender, has been encountered earlier than enlargement of the spleen. Nineteen patients had an enlarged liver on their first examination; 14 had an enlarged spleen; eight showed enlargement of both the liver and spleen on admission. This can readily be understood because of the function and physiology of the liver. On postmortem examination the spleen weighed over 200 grams in 30 of these cases. Infarction was present in 32, adhesions in one, congestion and edema in 22. In six cases, congestion and edema were the only findings. Six showed only postmortem changes. The liver at autopsy weighed over 1800 grams in 28 cases. Pathological changes were present in 45; these consisted of cloudy swelling and edema in 38, cloudy swelling alone in five, and chronic passive congestion alone in 17. Nutmeg liver was present in two as the only postmortem finding. Adhesions, liver scars, and acute hepatitis were each found once as the sole pathology present.

Petechiae were observed in 27 patients before death. Five of these patients also showed nodes of the toes, fingers or palmar surface.

Repeated examinations of the urine disclosed albumin in variable amounts in 26 patients, hyaline casts in 15, granular casts in nine, pus cells in 25, and red blood cells in 15.

Five of the 50 cases studied showed a positive Wassermann reaction before death, but none of these gave evidence on postmortem examination of syphilitic heart disease.

Summary

Fifty consecutive postmortem examinations of patients coming under my observation have been analyzed to determine the relative frequency of the symptoms complained of, the age incidence (12 per cent being under 10 years of age), and the pathological changes found on postmortem examination. It was found that subacute bacterial endocarditis is not as uncommon in childhood as previously thought, that pericarditis in its various forms is compatible with a diagnosis of subacute bacterial endocarditis, that bacteremia and an enlarged tender liver are more characteristic early symptoms than manifestations of infarction or enlargement of the spleen. Although but 23 showed old healed rheumatic endocarditis, all showed evidence of some previous myocardial damage. There was no congenitally deformed heart in this group. Three had old healed vegetations together with active infectious verrucae at the time of death, and two had recovered from this disease only to succumb to its sequelae.

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PERIARTERITIS NODOSA: WITH CASE REPORTS*

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A TOTAL of 101 cases of periarteritis nodosa reported in the English literature up to 1939 have been reviewed by Harris, Lynch and O'Hare.[1] To date there have been a total of 14 pathologically proved cases in more than 460,000 admissions at the University Hospital of the University of Michigan. Three of these have previously been reported,[2, 3] and the case histories of three others are to be published separately.[4, 5, 6] The remaining cases are herein summarized for the purpose of adding further clinical information regarding periarteritis nodosa.

In addition to the above mentioned 14 cases a number of other closely allied diseases have been seen, including such conditions as dermato-neuro-angiomyositis; atypical periarteritis nodosa, a proliferative arterial intimitis with generalized arterial disease and multiple organizing thrombi; purulent periarterial lymphangitis and arteritis; questionable periarteritis nodosa, necrotizing arteritis and periarteritis of small vessels throughout the body as well as in the kidneys, in addition to the changes of advanced arteriosclerotic nephropathy. Clinically as well as pathologically, it is sometimes exceedingly difficult to draw a distinct line of demarcation between these various processes.

ETIOLOGY

The etiology of periarteritis nodosa is unknown. Syphilis has been proved to have no causal relationship. Of the three cases of this group that had positive Kahn reactions, two (Cases 5 and 11) were considered to be false positive reactions since there was no history or evidence of syphilis. Postmortem examination revealed no definite evidence of the disease in the third case (Case 2) nor in Case 11. The virus theory of etiology [7, 8] has not been substantiated. The possible relationship of periarteritis nodosa to rheumatic fever cannot be disregarded.[9, 10, 11] The association of periarteritis nodosa and vegetative endocarditis has been reported.[12, 13, 14] Two of the University Hospital cases (Cases 4 and 7) had valvular endocarditis. Vining [15] considers the possibility that the rheumatic infection in certain instances acts as the sensitizing factor and prepares the way for the destructive attack by the infective agent of periarteritis nodosa. Cohen, Kline and Young [16] believe that periarteritis nodosa is a manifestation of clinical allergy so severe that irreversible and destructive lesions occur in the arterial walls and lead to disturbances in function of the organs supplied by the involved vessels. They consider every patient with severe allergy as a potential candidate for periarteritis nodosa. Other reports substantiate

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the frequency with which allergy is related.[17, 18, 19, 20] Harris, however, found allergy associated in periarteritis nodosa in only 15 per cent of the cases. Three patients presented in this report had an allergic history. Some claim periarteritis nodosa is not a disease sui generis but a hyperergic defensive reaction of the small muscular arteries and arterioles to a variety of toxic and infectious factors.[21, 12] This belief receives support by the frequency with which preceding or concomitant infections are seen in cases of periarteritis nodosa. The most generally accepted opinion at present is that the disease results from sepsis and is a complicating or superimposed lesion which is not the primary event.[22, 23, 24, 25] Spiegel[26] points out that infection frequently precedes the onset of periarteritis nodosa within the course of a few months and suggests that an etiologic relationship exists between the two conditions. Ten of the 14 cases herein described were considered to be related to some infection, which included gonorrhea, abscess, bronchiectasis, prostatitis, and severe upper respiratory disorders. It should be noted that in another case not included in these 10 (Case 9) necropsy showed chronic cholecystitis, which might possibly have been related to the periarteritis nodosa. The case of periarteritis and arteritis of the temporal vessels from which *Staphylococcus aureus* was cultured by MacDonald and Moser[27] may have been pathologically similar to cases of purulent periarterial lymphangitis and arteritis seen in other patients at the University Hospital but differing from periarteritis nodosa.

Pathological Changes

The protean nature of periarteritis nodosa can best be understood by realizing that it is a disease primarily of the arteries and one which affects secondarily the tissues or organs they supply.[28] It is an inflammatory reaction characterized by occlusion of the lumen as a result of thickening of the arterial wall, principally the media, or by thrombus; aneurysm formation; or rupture of the artery with hemorrhage.[29] Kussmaul and Maier[30] first described adequately the microscopic changes of the disease. Arkin[31] mentioned four progressive stages of changes in the arterial walls. The pathological process has been so well presented elsewhere that no further attempt to describe it will be made. The organs usually involved, in order of their frequency, are kidneys, heart, liver, gastrointestinal tract, mesenteric artery, muscles, spleen, lungs, and the peripheral and central nervous system.[1, 31] The arterial changes of periarteritis nodosa would probably be seen more often in the central and peripheral nervous system if routine postmortem examinations included a thorough study of these tissues. Secondary changes in the involved tissues are most frequently inflammation about the arteries, stasis, anemia, hemorrhage, edema, atrophy, fibrosis, infarction, and necrosis, depending upon whether the occlusion of the supplying artery was abrupt or sudden.

The pathological picture of periarteritis nodosa differs from that of dermato-neuro-angiomyositis only in the size of the vessels involved. The former ordinarily affects the middle-sized arteries, whereas the latter involves the smaller arteries and arterioles, with no one distinct line of demarcation. It is of interest to note that biopsies reported in Cases 10 and 11 were suggestive of angiomyositis; however, necropsy on Case 11 showed the middle-sized arteries more diseased than suspected from the biopsy. It is easily conceivable that arteries of both sizes and arterioles may be involved in the same case.

Table 1 shows the organs in which the microscopic vascular changes of periarteritis nodosa were found at necropsy. Only specimens of the heart,

TABLE I

Organs in Which Microscopic Vascular Changes of Periarteritis Nodosa Were Found on Postmortem Examination in Cases Reported

Case No.	Kidneys	G. I. tract including mesenteric arteries	Reproductive organs	Pancreas	Heart	Liver	Gall-bladder	Adrenals	Central nervous system	Lungs	Spleen
1	+	+	+	+	+	+	0	0	+	0	0
2	+	+	+	+	+	+	0	+	0	0	0
3	+	+	+	+	+	0	+	+	+	0	0
4	+	+	+	+	+	+	0	0	0	0	0
6	+	+	+	+	+	+	+	0	0	+	+
7	+	+	+	+	+	0	+	+	0	0	0
9	+	+	+	0	+	+	0	0	0	0	0
11	+	+	+	+	0	0	+	+	+	0	0
13					0	0				+	0
Av.	8/8 100%	8/8 100%	8/8 100%	7/8 88%	7/9 78%	5/9 54%	4/8 50%	4/8 50%	3/8 38%	2/9 22%	1/9 11%

liver, lungs, and spleen were sent to the pathologist in Case 13. In Case 5, examination of the gall-bladder after cholecystectomy revealed changes in the arteries characteristic of periarteritis nodosa. Muscle biopsies showed typical arterial changes in five cases ante mortem, although in Case 3 biopsies failed to demonstrate periarteritis nodosa. It must be remembered that more widespread involvement than is indicated here would likely be found if it were possible to examine each entire organ microscopically. Obviously many microscopic arterial changes are overlooked during routine postmortem examinations, and likewise many muscle biopsies may be reported as negative.

SIGNS AND SYMPTOMS

The signs and symptoms have been adequately reviewed by Harris, et al.[1] The 14 cases seen at the University Hospital are summarized in table 2. Cases 1, 2, and 4 were included in Harris' summary. Although the number of cases in the present series is obviously less than in Harris' group, it is felt that the percentages of symptoms listed are of significance since the entire

series reported is from the records of one hospital rather than a collection from reports in the literature which are not always complete in details. For instance, in the present series weakness was a symptom in 93 per cent of the cases, whereas Harris' review shows it in only 41 per cent.

TABLE II

A Summary of the Signs and Symptoms of Periarteritis Nodosa in the 14 Proved Cases Seen at the University Hospital

Case	Age	Sex	Race	Duration	Antemortem diagnosis	Previous or concomitant infection	Positive serology	History of allergy	Weakness	Fever	Tachycardia	Loss of weight	Hematuria	Dyspnea
1	46	M	W	7 mos.					+		+	+	+	+
2	16	M	C	?16 mos.		+	+							
3	48	M	W	10 mos.					+	+		+	+	+
4	47	M	W	11 mos.	+	+		+	+	+	+	+		+
5	39	M	W	7 mos.	+	+	?+		+	+	+	+	+	
6	65	M	W	?		+		+	+		+	+	+	+
7	15	F	W	5 wks.		+			+	+	+			+
8	51	F	W	17 mos.	+	+		+	+	+	+	+	+	+
9	62	M	W	?					+	+	+		+	+
10	50	M	W	27 mos.	+	+			+	+	+	+	+	
11	43	M	W	13 mos.	+		+		+	+	+			
12	49	M	W	15+ mos.	+	+			+	+		+	+	+
13	22	F	W	4 mos.		+			+	+	+	+	+	+
14	36	M	W	4+ mos.	+	+			+		+	+	+	
Av.	42	3F 11M	1C 13W	11.1 mos.	7 50%	10 71%	3 21%	3 21%	13 93%	10 71%	11 78%	10 71%	10 71%	9 64%

TABLE II (*Continued*)

Case	Age	Sex	Race	Duration	Neuritis, including muscle aches	Albuminuria	Leukocytosis	Anemia	Arthritis-pain and/or swelling in joints	Abdominal pain	Edema	Emaciation	Cough	Nausea
1	46	M	W	7 mos.	+	+	+		+	+		+	+	
2	16	M	C	?16 mos.					+					+
3	48	M	W	10 mos.	+	+	+	+		+	+	+		+
4	47	M	W	11 mos.	+		+	+	+	+	+	+	+	+
5	39	M	W	7 mos.	+	+	+	+	+	+	+	+		+
6	65	M	W	?	+	+					+	+	+	+
7	15	F	W	5 wks.				+	+	+			+	+
8	51	F	W	17 mos.		+	+	+	+	+		+		
9	62	M	W	?		+		+	+		+		+	+
10	50	M	W	27 mos.	+	+	+	+			+	+		
11	43	M	W	13 mos.	+		+	+	+	+	+			
12	49	M	W	15+ mos.	+	+							+	
13	22	F	W	4 mos.			+						+	
14	36	M	W	4+ mos.	+	+	+			+	+	+		+
Av.	42	3F 11M	1C 13W	11.1 mos.	9 64%	9 64%	9 64%	8 57%	8 57%	8 57%	8 57%	8 57%	7 50%	8 57%

TABLE II (*Continued*)

Case	Age	Sex	Race	Duration	Rapid onset	Hypertension	Headache	Atrophy	Uremia	Coma	Palpitation	Hematemesis or bloody stools	Eosinophilia	Sensory involvement
1	46	M	W	7 mos.		+			+					+
2	16	M	C	?16 mos.	?+		+		?+	+				
3	48	M	W	10 mos.	+	+	+	+			+	+	8%	+
4	47	M	W	11 mos.				+					63–77%	
5	39	M	W	7 mos.		+		+	+	+		+		
6	65	M	W	?		+	+	+	+	+	+	+	4%	+
7	15	F	W	5 wks.	+						+	+	4%	
8	51	F	W	17 mos.					+				20–23%	
9	62	M	W	?		+	+			+		+		
10	50	M	W	27 mos.	+	+		+	+	+			1–28%	+
11	43	M	W	13 mos.			+							+
12	49	M	W	15+ mos.	+		+	+			+		3–8%	
13	22	F	W	4 mos.	+						+			
14	36	M	W	4+ mos.	+	+	+	+				+		
Av.	42	3F 11M	1C 13W	11.1 mos.	7 50%	7 50%	7 50%	7 50%	6 43%	5 36%	5 36%	6 43%	5 36%	5 36%

TABLE II (*Continued*)

Case	Age	Sex	Race	Duration	Vomiting	Visual disturbances	Icterus	Purpura or other skin changes	Cyanosis	Nocturia	Pain or pressure in chest	Vertigo	Convulsions	Nodules
1	46	M	W	7 mos.			+			+	+			
2	16	M	C	?16 mos.	+								+	
3	48	M	W	10 mos.	+	+	+	+	+	+				
4	47	M	W	11 mos.				+						
5	39	M	W	7 mos.	+									
6	65	M	W	?					+					
7	15	F	W	5 wks.	+	+	+	+						
8	51	F	W	17 mos.		+								+
9	62	M	W	?					+					
10	50	M	W	27 mos.										
11	43	M	W	13 mos.		+				+		+		
12	49	M	W	15+ mos.			+							
13	22	F	W	4 mos.							+	+		
14	36	M	W	4+ mos.	+	+				+				+
Av.	42	3F 11M	1C 13W	11.1 mos.	5 36%	5 36%	4 28%	3 21%	3 21%	4 28%	2 14%	2 14%	1 7%	2 14%

Pain or swelling of joints or both was a complaint in a surprisingly large number (57 per cent) of the present review, but in the previous study it occurred in only 27 per cent of the patients. Of course, one could not defi-

nitely say that the joint symptoms were due to periarteritis nodosa in all instances, only one of which (Case 7) showed objective signs of joint involvement. Eight of the patients of the present series had some nausea during their illness, although this was previously reported in only 17 per cent of the cases. Other symptoms with higher percentages in the present series are weight loss, neuritis, hematuria, dyspnea, emaciation, cough, atrophy, icterus, and headache. A comparison of the frequency of signs and symptoms as recorded by Harris and as seen in the present series is shown in table 3.

TABLE III

A Comparison of the Frequency of Signs and Symptoms of Periarteritis Nodosa as Recorded by Harris and as Seen in the Proved Cases at the University Hospital

	Harris %	Univ. Hosp. %		Harris %	Univ. Hosp. %
Weakness	41	93	Headache	29	50
Tachycardia		78	Atrophy	25	50
Fever	80	71	Uremia		43
Loss of weight	48	71	Hematemesis or bloody stools		43
Hematuria	47	71	Coma		36
Dyspnea	41	64	Palpitation		36
Neuritis	48	64	Eosinophilia	19	36
Albuminuria	65	64	Sensory involvement	31	36
Leukocytosis	70	64	Vomiting	31	36
Anemia		57	Visual disturbances	23	36
Arthritis	27	57	Icterus	12	28
Abdominal pain	57	57	Nocturia		28
Edema	52	57	Purpura or other skin changes	22	21
Emaciation	36	57	Cyanosis	21	21
Nausea	17	57	Pain in chest	16	14
Cough	36	50	Vertigo	8	14
Rapid onset	58	50	Nodules	16	14
Hypertension	46	50	Convulsions	15	7

The ratio of 11 males to three females in the group now reported coincides with the previous report of three to one. The average age of 42 years was slightly higher than the previously reported average of 36.9 years. The average duration of the illness of 11.1 months is longer than that of 8.6 months previously reported. The duration of illness in Cases 6 and 9 could not be accurately estimated on account of the history of known high blood pressure for three and five years respectively and because of the possibility of all symptoms being due to the hypertension. If the hypertension in these cases was due to periarteritis nodosa, the disease of necessity would be of longer duration than previous average estimates. Among the constitutional symptoms, weakness was the most common. Leishman [33] lists it as one of the common symptoms. Tachycardia and fever were present in 11 and 10 cases, respectively. The fever is usually low-grade, below 101°, although in Case 10 it rose to as high as 104°. Boyd and Nussbaum [21] point out that tachycardia disproportionately rapid for the body temperature is suggestive of periarteritis nodosa. Weight loss, in some cases exceeding 50 pounds,

was present in 10 of the cases, or 71 per cent. Leukocytosis is common, and a significant eosinophilia (8 per cent or higher) was seen in five of the 14 cases. Eight of the patients had anemia. Emaciation and atrophy are frequently observed. The onset of the illness was considered acute in six, and questionably so in a seventh case.

Among the cardio-respiratory symptoms, in addition to the tachycardia, are dyspnea, palpitation, cough, edema, and a feeling of pain or pressure in the chest. It is interesting to note that Case 13, without cardiac involvement, had all these symptoms except edema. The periarteritis nodosa in this case affected the pulmonary vessels. With the vessels of the heart diseased as frequently as they are, one would expect cardio-respiratory symptoms to occur frequently.

Signs of gastrointestinal tract involvement included abdominal pain, nausea, and vomiting. These were considered serious enough in Case 5 to warrant laparotomy and cholecystectomy, without which the antemortem diagnosis would not have been made. Not only cholecystectomy but also appendectomy and nephrectomy have been performed as a result of mistaken antemortem diagnoses.[26, 32, 34, 35] Several instances of intra-abdominal aneurysm with perforation and resultant symptoms have been reported.[34, 35, 36] Six of the 14 patients presented here had gastrointestinal hemorrhage as evidenced by hematemesis or the presence of blood in the stools. Pass [39] found only 52 cases of anemic infarction of the liver reported in the English literature up to 1935; periarteritis nodosa was the most common cause of the condition. A few other cases have been reported since.[40] Arkin's Case 5 showed "hepar lobatum" believed to be caused by periarteritis nodosa. Case 6 of this group showed a healed infarct of the liver on postmortem examination. Four cases of the present series had some icterus, most marked (Case 12) when an associated enlargement of the liver was present. The jaundice later disappeared, and the liver receded in size. It seems probable that this patient had a single large infarct or multiple small ones. In two cases (Cases 7 and 8) the spleen was palpable,[47] although in only one case (Case 6) were the arteries of this viscus found involved. Middleton and McCarter [11] presented a case with a glucose tolerance test interpreted as diabetic in which postmortem examination showed periarteritis nodosa involving the pancreas. The glucose tolerance test in Case 10 was of the diabetic type.

Signs and symptoms referable to the genito-urinary tract are frequent. Among the evidences of kidney damage observed are hypertension, hematuria, albuminuria, nocturia, edema, uremia, and coma. Casts are frequently present in the urine. Five of the cases presented here and questionably a sixth had uremia, and five became comatose prior to death. It is interesting to note that in addition to Cases 6 and 9 with typical histories of essential hypertension and no symptoms suggestive of other complications, several similar cases have been seen in which necropsy revealed a questionable periarteritis nodosa, but not sufficiently definite to be included in this

report. Only time will tell whether the last blood pressure recording of 148 mm. Hg systolic and 94 mm. diastolic in Case 12 is an indication of developing hypertension. Keegan [32] reports a case in which a right nephrectomy was performed and the kidney showed periarteritis nodosa. The patient died two months later, at which time the other kidney had the changes of early arteriosclerosis and chronic vascular nephritis. He postulated that many cases of chronic vascular nephritis may have their origin in mild renal periarteritis nodosa. This seems quite possible and may be substantiated by the finding of both periarteritis nodosa and arterio- and arteriolosclerotic nephropathy in a number of cases on postmortem examination (Cases 6 and 9). The diagnosis in Case 14 was definitely established only after splanchnicectomy for a supposed malignant hypertension. The frequency of genito-urinary tract symptoms is easily understood when one realizes the frequency of involvement not only of the kidneys but also of various organs of reproduction, including the testes, seminal vesicles, prostate, epididymes, salpinges, and ovaries. The testicular pain reported in Case 12 was most likely on the basis of disease of the vessels of the testes.

Nervous system involvement may be indicated by headache, neuritis, muscular atrophy, sensory changes in the form of anesthesias and paresthesias, visual disturbances, vertigo, and convulsions. Neuritis, including muscle aches, was present in nine cases. The most completely studied case in the English literature showing sensory changes during the course of periarteritis nodosa is that of Fitz, Parks, and Branch.[37] Eyeground changes, as those in Case 3, have been previously reported with examinations showing periarteritis nodosa of the vessels of the eye.[12, 25, 38] Bernstein [38] reports a case of progressive nerve deafness of periarteritis nodosa origin. The deafness in Case 10 seems to be another such case.

Skin lesions in periarteritis nodosa have been quite varied. One of the most interesting examples is the case in which the diagnosis during life was disseminated lupus erythematosus but the necropsy showed periarteritis nodosa.[42] An erythematous eruption appeared in Case 3. Dunbar [41] presented a case of periarteritis nodosa with associated thrombocytopenic purpura. Case 7 had purpura hemorrhagica. Several cases of gangrene and ulceration on the extremities have been reported.[13, 14] Case 4 had an ulcerated elbow. Subcutaneous nodules, previously considered as diagnostic of the disease, occurred in only two cases (Cases 8 and 14).

Treatment

One must conclude, with Harris, et al., that there is no specific treatment for periarteritis nodosa. Cases 2 and 4 received adequate neoarsphenamine therapy without benefit.[44, 45] Case 10 remained afebrile while receiving sulfanilamide, and had the longest duration of disease of the cases reported. He was afebrile, however, for five days before taking the drug. Case 12 took small doses of sulfanilamide and is still alive, but this could not pos-

sibly be attributed to the drug. Case 11 was given adequate treatment with sulfanilamide and died 13 months after the onset of symptoms. Since there is no known treatment and there is so often an associated infection, it seems justifiable to give sulfanilamide or sulfapyridine until an adequate number of cases have been accumulated from which conclusions may be drawn.

Prognosis

Twelve of the 14 patients in the present series are dead, although five left the hospital alive. Two recent cases reported [37] indicate a duration of life of eight and six years after the onset of symptoms. These would raise Harris' [1] average duration of illness considerably. The longest duration of the disease actually reported is 12 years.[46] Such reports of longevity of patients with the disease are rare. The longest known duration of life of the 14 cases reported here is 27 months (Case 10). Case 7 apparently lived only five weeks after the onset of symptoms caused by periarteritis nodosa. One must conclude that the prognosis is extremely poor, although Case 12 is alive and nearly asymptomatic at the present time, and Case 14 is living. It is conceivable that mild cases may remain undiagnosed and live considerably longer than present reports indicate.

Summary and Conclusions

To date 14 proved cases of periarteritis nodosa have been observed at the University Hospital. Their signs and symptoms have been summarized. Seven of the 14 cases had antemortem diagnoses of periarteritis nodosa. Such a diagnosis can be proved only by positive biopsy report, although negative biopsy reports do not rule out the diagnosis.

The symptoms are varied as arteries in any portion of the body may be involved. The most common symptoms are referable to the organs most commonly affected.

The duration of the illness is closely correlated with the degree of involvement of the vital organs and resultant impairment of function of those organs. The average length of life after the onset of illness in this group of cases was 11.1 months.

Although the etiology of periarteritis nodosa is unknown, the close relationship between the disease and previous and concomitant infections is noted.

There is no specific treatment. The prognosis is poor. Only two of the 14 cases of this series are alive at the time of writing.

Case Reports

Case 1. J. B., admitted on October 9, 1930, was previously reported by Hauser.[2] Outstanding features of this case were epigastric pain, weakness, loss of weight, joint pains, paresthesia, hypertension, pain in the right side of the chest, dyspnea,

albuminuria, and uremia. Antemortem diagnosis was chronic glomerulo-nephritis but postmortem examination showed diffuse periarteritis nodosa.

Case 2. J. L. B., observed on September 1, 1931, was also previously reported by Hauser.[2] The outstanding features were swelling and pain in the right side of the face, headache, vomiting, ulceration of nasopharynx, convulsion, and coma. The patient had a positive blood Kahn reaction. Antemortem diagnoses had been tertiary syphilis and luetic osteomyelitis of the maxillae and palate. He had received intensive bismuth and arsphenamine antiluetic therapy. Necropsy showed periarteritis nodosa but no evidence of syphilis.

Case 3. J. F., a 48-year-old white male, was first admitted to the hospital on August 1, 1932, with a history of nausea, vomiting, chills, fever, and night sweats occurring on December 25, 1931, after an alcoholic debauch, with the onset of pain in the calves of his legs three days later. Shortly afterward he had difficulty in walking, a staggering gait, and numbness and tingling of the toes and feet. In April, 1932 he noted swelling of his feet and ankles, palpitation, dyspnea, and nocturia. Prior to admission to the hospital, some friends observed that he was jaundiced. At the age of 19 years he had had gonorrhea and a "soft chancre" for which some "arm injections" were given although he was not told that he had syphilis. There was a brown ulcerating lesion on his neck for one year.

Physical examination revealed a well developed, well nourished adult white male, not acutely ill, but with slightly icteric skin. Temperature was 100°, pulse 84 per minute, respirations normal, and blood pressure 190 mm. Hg systolic and 112 mm. diastolic. There was a brown ulcerated lesion on the neck. The heart was enlarged to 11 cm. to the left of the midsternal line. A systolic murmur was present at the apex. Râles were heard in the left posterior midscapular region. The radial arteries were tortuous but not beaded. There was pitting edema of the feet and ankles. The Achilles jerk was absent bilaterally, and plantar stimulation caused no flexion on either side. Gait was slow and ataxic.

The blood Kahn reaction was negative. The spinal fluid Kahn reaction was also negative; total spinal fluid protein was increased to 79 mg. per 100 c.c., and the globulin was 3 plus. The colloidal gold curve was 0011100000, and mastic curve was 221100. The spinal fluid was clear with no cells present. Urinalyses showed an occasional trace of albumin and a rare red blood cell. The hemoglobin was 80 per cent with white blood cell counts ranging from 10,800 to 14,000 per cubic millimeter. The differential counts were normal except for an 8 per cent eosinophilia on two occasions. The renal function tests were normal. The blood non-protein nitrogen, the basal metabolic rate, and agglutinations for the typhoid-dysentery-brucella groups were also normal. The blood culture was negative. The electrocardiogram showed slightly inverted T-waves in Lead II; sharply inverted T-waves in Lead III; and small Q-waves in all leads. Chest roentgen-ray showed elongation of the aorta and increased peritruncal markings. Gastrocnemius biopsy report was "marked degenerative changes in the voluntary muscle. Zenker's necrosis. Interstitial myositis, but no significant eosinophilia in the infiltrations. . . . This is a degenerative myositis of some . . . unknown etiology. No trichinosis." (Dr. C. V. Weller.) Biopsy of the deltoid muscle revealed nothing abnormal. Pathological report on the lesion removed from the neck was "squamous cell carcinoma of the mediocellular type. Ulcerating secondarily infected surface." (Dr. C. V. Weller.)

While in the hospital there were daily temperature elevations often as high as 101 degrees. The pulse averaged 85 per minute. The slightly icteric tint disappeared. Ophthalmoscopic examination showed arteriosclerosis of the retinal vessels with a few small retinal hemorrhages. Roentgen-ray therapy was applied to the site of removal of the carcinoma of the neck. His condition was reported as somewhat improved when he was discharged on July 15, 1932 with final diagnoses of essential hypertension,

fever of unexplained etiology, peripheral polyneuritis, interstitial myositis, and carcinoma of the neck.

He was readmitted on October 18, 1932 with the interval history of slight diminution of previous symptoms but with recent fatigue, epigastric distress, blurring of vision, temporal and occipital headaches, loss of 50 pounds in weight, weakness, wasting of arms and legs, and stinging sensations in the balls of the feet and toes.

Physical examination then revealed an emaciated male with marked muscular atrophy. Blood pressure was 240 mm. Hg systolic and 150 mm. diastolic. There was an erythematous eruption over the lower portion of the chest and upper abdomen. Ophthalmoscopic examination showed advanced albuminuric retinitis with numerous hemorrhagic areas. There was diminution of the senses of touch, position, pain, and temperature below the knees. Otherwise, findings were essentially the same as on the previous admission.

The spinal fluid Kahn reaction remained negative; the globulin was 4+; the colloidal gold curve was 4234311000, and the mastic 332210. The spinal fluid was clear with about 10 red blood cells per cubic millimeter. The spinal fluid pressure was normal. Urinalysis showed a one plus albuminuria with a few red cells and occasional hyalin and granular casts. Blood examination revealed a hemoglobin of 68 per cent and a white blood cell count of 14,000 per cubic millimeter with a normal differential count. Gastric analysis showed a slight amount of hydrochloric acid. The blood non-protein nitrogen was normal on October 20. Roentgen-rays showed a normal upper gastrointestinal tract and a moderate generalized osteoporosis.

During the hospital course, the patient's condition become worse, with persistent epigastric distress, hiccoughing, and a dark brown hematemesis on October 31, followed by bilateral râles, increasing dyspnea, and cyanosis. Respirations ceased on November 1, 1932. In addition to the previous diagnoses a metastatic neoplasm was strongly suspected.

Necropsy disclosed periarteritis nodosa involving the arteries of the brain, heart, trachea, entire gastrointestinal tract, pancreas, gall-bladder, adrenals, kidneys (old ruptured aneurysm in one branch of renal artery), testes, seminal vesicles, and within the nerve bundle of the left common peroneal nerve; generalized arteriosclerosis; old area of softening in the basal ganglia; localized renal atrophy; marked left ventricular hypertrophy and terminal cardiac failure with right-sided dilatation; early purulent bronchitis and bronchopneumonia; diffuse fibrous atrophy of right testis; scattered subserous and submucosal petechial hemorrhages; passive congestion and parenchymatous degeneration of all organs; no metastatic lesions. (Dr. B. M. Hathaway.)

Case 4. E. R., admitted on August 17, 1932, has previously been reported by Curtis and Coffey.[3] The outstanding features of this case were pain in the arms and legs, anorexia, loss of weight, nausea, weakness, generalized atrophy, edema of the hands and feet, secondary anemia, leukocytosis, and eosinophilia as high as 77 per cent. The diagnosis in this case was recognized prior to necropsy.

Case 5. R. H., a 39-year-old white male, entered the hospital on January 6, 1934, with a history of a loss of 54 pounds in weight, loss of strength, and a constant abdominal ache. In July, 1933, he had had a polyarticular arthritis with swollen, painful joints for one month, edema of the legs, and enlargement of the liver. All of his teeth had been extracted. His symptoms disappeared until November, 1933, when he was chilled on a hunting trip. Two days later a dull, persistent generalized abdominal ache appeared which was not related to meals. He became constipated, and five weeks prior to admission developed an intermittent, low-grade fever. There was no history of primary or secondary syphilis. He had previously been in good health.

Physical examination revealed a well developed, poorly nourished white male with warm skin, facial flush, and sunken cheeks. Temperature was 100.4°; pulse, 90 per

minute; respirations, 20 per minute; and blood pressure, 150 mm. Hg systolic and 96 mm. diastolic. The patient was edentulous and had a post-nasal discharge. There was a soft systolic apical murmur. The pulse was forceful, and the second aortic valve sound was loud. Lungs were normal. The recti muscles were quite tense, especially in the upper abdomen, which made thorough abdominal examination impossible. There did not appear to be any abdominal tenderness. There was marked atrophy of the extremities with muscle tenderness. Costovertebral angle tenderness was present bilaterally. The prostate was tender but otherwise normal.

One Kahn reaction was two plus positive, one was one plus positive, and two were negative. Several urinalyses prior to January 31 were negative except for a rare red blood cell. After that date, however, urinalyses on a number of occasions showed a two plus albuminuria with occasional granular casts and red cells. The hemoglobin was 75 per cent. White blood cell count varied from 11,940 to 26,300 per cubic millimeter with normal differential counts, which did not show at any time more than 2 per cent eosinophiles. Blood culture was negative. Blood bilirubin was 2.5 milligrams per 1,000 c.c. (indirect). Between January 26 and February 12, the blood non-protein nitrogen rose from 38.2 to 114.5 milligrams per 100 c.c. Electrocardiogram was normal. Prostatic smear contained innumerable pus cells, although the patient gave no history of infection. Roentgen-ray examinations showed faint visualization of a distended gall-bladder, an enlarged liver, and normal chest, upper gastrointestinal tract, and colon.

As the gall-bladder showed only faint visualization and was distended enough to reach the right iliac crest, and since no other diagnosis was established, this patient had an exploratory laparotomy and cholecystectomy on January 15. At this time the liver was found somewhat hard but no other abnormality was noticed. The report of the pathologist following cholecystectomy was: "No cholecystitis in the ordinary sense. Many of the medium-sized arteries show various stages of medial necrosis and productive as well as exudative periarteritis. This patient probably has a systemic arterial disease, belonging in the general group of periarteritis nodosa." (Dr. C. V. Weller.) The wound was well healed by January 27. The temperature rose as high as 102.4° during the hospital course, with the pulse ranging between 84 and 122 per minute. The patient's symptoms continued and consisted chiefly of pains in the back of his neck and in his extremities. On some occasions he vomited material which contained fresh blood. He became irrational on February 9 and semi-comatose on February 10; respirations became Cheyne-Stokes in type. He was removed from the hospital against advice on February 12, with final diagnoses of periarteritis nodosa, subacute nephritis, hypertension, uremia, secondary anemia, and chronic prostatitis. Death occurred outside the hospital on February 22, 1934. No necropsy was performed.

Case 6. E. A., a 65-year-old white male, entered the hospital on August 22, 1934, with the chief complaints of shortness of breath and swelling of the feet and ankles. He had suffered from mild asthmatic attacks for 25 years. Fourteen years ago he had been told he had heart trouble, and three years ago it was discovered that he had hypertension. He had been asymptomatic, however, until the winter prior to admission when he observed dyspnea on slight exertion, headaches, weakness, cough productive of sputum, sometimes bloody, and weight loss. For the last few weeks he had noticed occasional "fluttering" in his heart, and one week prior to admission he first became aware of swelling of his feet and ankles. For 10 weeks he had experienced a severe diarrhea with frequent stools which were sometimes bloody, with gaseous distention and nausea. There was a history of gonorrhea 25 years previously with several exacerbations since. Owing to the patient's confused mental condition it was not possible to obtain a more reliable history.

Physical examination revealed a poorly nourished, dehydrated, elderly white male, quite dyspneic at bed rest. Temperature was 98°; respirations, 30 per minute; and

blood pressure, 150 mm. Hg systolic and 110 mm. diastolic. The skin was dry, deeply pigmented, and parchment-like. The lips were slightly cyanotic. The teeth were in extremely poor condition with root fragments remaining. There was engorgement of the cervical veins. The thorax was emphysematous, and there were numerous musical râles throughout both lung fields with a prolonged expiratory phase. Inconstant râles could be heard in both lung bases. The left border of cardiac dullness was 14 cm. to the left of the midsternal line. There was auricular fibrillation with a pulse deficit, the apex rate being 114 per minute and the radial pulse 78 per minute. A loud, harsh, systolic murmur was heard best at the apex. The peripheral vessels were markedly sclerotic. The firm, slightly tender liver edge extended to the umbilicus. Moderate edema of the ankles was present. All reflexes were diminished, and there was diminution in sensation over the right forearm. The muscles showed extensive atrophy.

The Kahn reaction was negative. The blood examination showed 90 per cent hemoglobin and a white blood cell count of 8,200 per cubic millimeter with normal differential, showing 4 per cent eosinophiles. A one plus albuminuria was present and the urinary sediment showed 2 to 3 red blood cells and 2 to 3 white blood cells per high power field. The stool examination revealed a three plus guaiac reaction. The blood non-protein nitrogen was 55.5 mg. per 100 c.c.

The patient was given two injections of 0.016 gm. morphine sulfate during the first eight hours of hospitalization. Eleven hours after admission respirations had dropped to 5 to 8 per minute. Digifolin was administered intravenously and digitalis was given by mouth. Several doses of caffeine sodio-benzoate were injected. He became comatose and cyanotic with labored respirations. His course was progressively downhill and he died 33 hours after admission to the hospital. Antemortem diagnoses were arteriosclerotic and hypertensive heart disease with auricular fibrillation and cardiac enlargement, cerebral arteriosclerosis, bronchial asthma, pulmonary emphysema, and hypertrophic arthritis of the spine.

Necropsy showed periarteritis nodosa involving the coronary, pulmonary, bronchial, diaphragmatic, splenic, mesenteric, pancreatic, hepatic, cholecystic, renal, testicular, prostatic, and other arteries; multiple healed myocardial infarcts; old sclerosing epicarditis; hydropericardium; bilateral hydrothorax; ascites; acute exacerbation of chronic passive congestion of all organs; acute pulmonary edema; old healed pulmonary tuberculosis and adhesive pleuritis; generalized arteriosclerosis; arterio- and arteriolosclerotic nephropathy; fibroid atrophy of the testes; healed infarct of liver; old leptomeningeal thickening (no periarteritis nodosa of meningeal, spinal, or cerebral arteries). (Dr. J. C. Bugher.)

Case 7. L. W., a 15-year-old white female, was admitted on August 13, 1935, with chief complaints of weakness and cough. Since she had whooping cough at the age of 9 months, there had been a cough productive of small amounts of sputum which was never bloody. The cough had been worse for the last four or five years, but otherwise the patient had felt well. About five weeks prior to admission she developed pain in both ankles without swelling or redness. This spread to the knees, right shoulder, little finger of the right hand, and index and ring fingers of the left hand. For four weeks she had had some fever, easy fatigability, palpitation, and shortness of breath on mild exertion. Pallor became pronounced, and the patient had a more productive cough with blood-streaked sputum. Recently she had complained of sore throat and soreness of the tongue. For the last week or so the patient had complained of dull left upper quadrant pain which radiated across the abdomen. There had been ecchymosis and swelling of the right eye for one day.

Physical examination revealed a strikingly dyspneic adolescent female who appeared acutely ill with pallor and a yellowish tinge. The temperature was 101.8°; pulse, 138 per minute; respirations, 38 per minute; and blood pressure, 118 mm. Hg

systolic and 40 mm. diastolic. There was an area of ecchymosis and swelling of the upper and lower eyelids on the right. In the left auricle was a small area with crusted blood. The patient had a slight mucopurulent nasal discharge. The postpharyngeal wall was reddened. The breath sounds were harsh with a few coarse rhonchi on coughing. The lungs were otherwise normal. The left border of cardiac dullness was 10 cm. to the left of the midsternal line. A systolic murmur was heard at the apex, and the apex beat was forceful. The spleen was palpable just below the left costal margin. There was clubbing of the fingers and toes, with fusiform swelling of the interphalangeal joints of the right fifth and left second and fourth fingers, and periarticular swelling of the knees. The reflexes of the lower extremities were diminished bilaterally. Numerous hypertrophic papular crusted lesions were present over both elbows and the medial aspects of both knees.

The Kahn reaction was negative. Blood culture showed no growth. Hemoglobin was 30 per cent; red blood cell count was 1,750,000 per cubic millimeter; white blood cell count was 8,900 per cubic millimeter with a normal differential count. Two sputum examinations were negative for tubercle bacilli. The electrocardiogram was not definitely abnormal aside from a tachycardia of 120 per minute. No urinalysis was recorded. Chest roentgen-ray showed an acute exudative bilateral pulmonary lesion, conglomerate in certain areas without marked pleural reaction, with one calcareous peribronchial node at the right hilum, considered strongly suggestive of diffuse active tuberculosis.

The patient was given a blood transfusion and treated symptomatically. Her condition became worse, and about 30 hours after hospital admission she had a coughing spell, vomited a small amount of blood, had a small pulmonary hemorrhage, and respirations ceased. Antemortem diagnoses were probable subacute bacterial endocarditis, bilateral bronchiectasis and lung abscesses, infectious arthritis, septicemia, and secondary anemia.

Necropsy revealed generalized arterial disease; periarteritis nodosa of arteries of the pancreas, gall-bladder, adrenals, kidneys, fallopian tubes, heart and elsewhere in the body; late subacute glomerulonephritis; acute aortic valvular endocarditis; acute necrotizing laryngitis and tracheitis; chronic fibrocaseous bronchitis and peribronchitis; old fibrocaseous tuberculosis of bronchial nodes; cylindrical bronchiectasis; subacute ulcerative jejunitis (tuberculous?); multiple hemorrhages in lungs; petechial hemorrhages in skin, conjunctiva, gastrointestinal mucosa, and beneath peritoneum and pericardium; purpura hemorrhagica; terminal acute purulent lobular pneumonia; acute passive congestion of all organs; terminal right-sided cardiac dilatation with relative tricuspid insufficiency; pulmonary edema; ascites; chronic adhesive perisplenitis; agonal dissemination of gas-forming organisms; chronic pulmonary osteoarthropathy. (Dr. C. V. Weller.)

Case 8. A. H., a 51-year-old white female, was admitted to the hospital on October 14, 1935, with a history of having had the "grippe" and "congestion of the lungs" 16 months previously, with fever during the summer of 1934. She had since noticed weakness, and had developed an infection and swelling of the nose and suffered from a three-day attack of abdominal pain. Four months prior to admission there had been the onset of pain in the eyes, associated with redness. There had been a loss of 50 pounds in weight, shortness of breath, and swelling and soreness of ankles, knees, and hips. The patient had had asthma from the age of 3 to 13 years. Prior to admission to the hospital she had had an eosinophilia of 20 per cent and a muscle biopsy for suspected trichinosis. The biopsy was reported as showing periarteritis nodosa and the patient was sent to the hospital for substantiation of the diagnosis.

Physical examination showed a pale, malnourished, apparently chronically ill white woman with photophobia. Temperature was 99.6°; pulse, 100 per minute; respirations, 20 per minute; and blood pressure, 120 mm. Hg systolic and 90 mm. diastolic.

The breath was uriniferous. There was circumcorneal conjunctival hyperemia with multiple small half-pinhead sized areas of infiltration of the conjunctiva. Heart and lungs were normal. The spleen was palpable on deep inspiration. There were "shot-sized" nodules over both elbows, red, non-tender, firm, and crusted at their surfaces.

The Kahn reaction was negative. Multiple urinalyses showed albuminuria, red blood cells, and white blood cells. The hemoglobin was 55 per cent; white blood cell count 11,700 per cubic millimeter, and 14,500 on two occasions with 20 per cent and 23 per cent eosinophilia, respectively. Stool examination was normal. Blood urea nitrogen was 60 mg. per 100 c.c., and the urea clearance test showed only 10.9 per cent and 9.6 per cent of normal function in the first two hours, respectively. The pathological report on the previously obtained muscle biopsy confirmed the previous pathological report of periarteritis nodosa: "The nutrient arteries and arterioles exhibit marked changes in various stages. There is necrosis of artery wall with a very marked periarterial inflammatory infiltration, polyblast formation, and fibroblastic reaction. In a somewhat later stage thrombosis occurs and this in turn is followed by organization. These are the changes of a primary disease of the smaller arteries closely resembling periarteritis nodosa as it occurs in arteries of a somewhat larger order." (Dr. C. V. Weller.)

The patient remained in the hospital until October 20, and was treated symptomatically. Her condition remained unchanged during the hospital stay. Pulse averaged 90 per minute and there was a low-grade afternoon fever to 100°. Final diagnoses were periarteritis nodosa, secondary anemia, splenomegaly, and eczematous keratoconjunctivitis.

Death occurred outside the hospital on November 16, 1935, according to her referring physician, with edema of the lungs and pneumonia.

Case 9. E. M., a 62-year-old white male, entered the hospital on May 8, 1936, having had known high blood pressure with mild headaches for 5 or 6 years. In January, 1935, he had the onset of shortness of breath on exertion and ease of fatigue. The following October he observed the progressive development of orthopnea, edema of feet and ankles, cough, and weakness. One month prior to admission his hands began to swell, and he noticed one tarry stool six weeks previously. The patient's responses were not considered altogether reliable. He had been treated by his referring physician for arthritis.

Physical examination revealed a dyspneic and orthopneic, drowsy, acutely and chronically ill, elderly appearing, white male. Temperature was 99°; pulse, 102 per minute; respirations, 24 per minute; and blood pressure, 210 mm. Hg systolic and 150 mm. diastolic. There was cervical venous engorgement. Funduscopic examination showed arteriovenous nicking with generalized edema of the retina. Râles were heard in both lung bases. The heart was enlarged to 13 cm. to the left of the midsternal line. There was a systolic precordial murmur. The heart sounds were distant. The peripheral vessels were sclerotic. The abdomen was enlarged, with shifting dullness, and there was pitting edema of the lower anterior abdominal wall, the scrotum, both lower extremities, and the hands. There was slight cyanosis of the nails.

The Kahn reaction was negative. Urinalysis showed a 4+ albuminuria with white blood cells, red blood cells, and finely and coarsely granular casts. Hemoglobin was 67 per cent and white blood count 6,400 per cubic millimeter with a normal differential count. Stool examination was normal. Blood non-protein nitrogen was 39.7 mg. per 100 c.c. Electrocardiogram on May 8 showed definite left axis deviation with T-waves slightly inverted in Lead I and on May 16, auricular fibrillation with A–V dissociation and ventricular extrasystoles causing perfect bigeminy, which suggested digitalis intoxication.

The patient was placed on a neutral diet with ammonium chloride and mercupurine, digitalis, morphine sulfate, and aminophyllin, with loss of 15 pounds of edema

in six days, after which he developed increased weakness and drowsiness. Death occurred on May 16, 1936. Temperature had varied from normal to 101°, and pulse from 66 to 114, averaging 90 per minute. The clinical diagnoses were essential hypertension, generalized arteriosclerosis, hypertensive and arteriosclerotic heart disease with congestive failure, and secondary nephritis.

Necropsy showed systemic arterial disease, periarteritis nodosa, involving chiefly the liver, the retroperitoneal tissues, intestine, and epididymis, with one small subepicardial vessel which showed a nodular eccentric perivascular proliferation; generalized arteriosclerosis; old anemic infarction of brain; arterio- and arteriolosclerotic nephropathy; cardiac hypertrophy, most marked in the left ventricle; subendocardial fatty infiltration; terminal cardiac dilatation; nutmeg liver; chronic passive congestion of lungs; anasarca; ascites; hydropericardium; chronic cholecystitis and cholelithiasis. (Dr. C. V. Weller.)

Case 10. T. K., a 50-year-old white male, was admitted to the hospital on February 21, 1938, with the chief complaint of numbness and tingling of the legs and feet. About five months prior to admission, he first noticed a burning type of pain in his feet which spread to his legs and knees, followed by difficulty in walking, weakness, numbness, and tingling. There was a weight loss of 33 pounds and fever almost daily. As long as the patient remained at rest the pains disappeared. The patient had been impotent for four to six months.

Physical examination revealed a well developed white adult male showing signs of weight loss and generalized muscular atrophy. Temperature was 101°; pulse, 108 per minute; respirations, 20 per minute; and blood pressure, 102 mm. Hg systolic and 60 mm. diastolic. There was slight pitting edema of the ankles. Vibration sense was diminished at the ankles, and there was mild hypalgesia over both feet. Moderate pallor of the mucous membranes was present. Râles were heard in the left posterior lung field. The left testicle was atrophied, and the right was small and soft.

The Kahn reaction was negative. Of five urinalyses, one showed a trace of albumin, and all showed red blood cells and hyalin and granular casts. Numerous hemoglobin determinations varied from 39 to 60 per cent and white blood cell counts from 10,000 to 18,000 per cubic millimeter. Differential counts showed from 1 to 28 per cent eosinophilia. No malarial organisms could be found. Bromsulphalein test for liver function and gastric analysis were normal. Blood non-protein nitrogen was 51 mg. per cent, and the urea clearance test showed 26 per cent and 38 per cent of normal in the first two hour specimens. Total serum proteins were 7.2 per cent with an A/G ratio of 0.4. Blood bilirubin was normal, and the glucose tolerance test showed a fasting blood sugar of 92 mg. per cent; two hour specimen, 182 mg. per cent; three hours, 214 mg. per cent; and four hours, 156 mg. per cent. Repeated blood and stool cultures and agglutinations were normal. Chest roentgen-rays showed no abnormalities except an old left basilar pleuritis. Pyelograms, and roentgenograms of the legs, feet, gastrointestinal tract, and gall-bladder were normal. Electrocardiograms were essentially normal. Biopsies of the deltoid and gastrocnemius muscles were reported "Well marked atrophy. . . . The largest arteriole in this specimen has an eccentric perivascular lymphocytic infiltration . . . strongly suggestive of periarteritis nodosa." . . . "Very severe periarteritis involving the smaller vessels, some of which show localized necrosis of their wall. Patchy atrophy in the voluntary muscle. Angiomyositis, so-called. No evidence of trichinosis." (Dr. C. V. Weller.)

For the first four days of hospitalization the patient had a daily fever ranging from 101 to 104°, following which he was afebrile for five days, when again there was a daily fever to 101° for five days. At this time the patient was started on sulfanilamide for 10 days, during which he was entirely afebrile. When the sulfanilamide was discontinued there was again daily fever to 100 or 101°. The patient had a chronic upper respiratory infection with much hoarseness, and there was an inter-

mittent progressive deafness. He was given vitamin supplements, blood transfusions, ferrous sulfate, and symptomatic care. There was some improvement at the time of discharge on April 15. The pulse averaged 100 per minute.

The patient was readmitted to the hospital on May 16, 1938 in a somewhat improved condition. Some of the previous symptoms persisted, and he complained of weakness and stated that his feet were always cold. Physical examination was essentially the same as previously except that there was no edema. The blood pressure was 100 mm. Hg systolic and 65 mm. diastolic. Urea clearance test showed 45 per cent and 37 per cent of normal function in the first two hours, respectively, and blood non-protein nitrogen was 125 mg. per cent. Urinalysis revealed 2 + albuminuria, and hemoglobin was 44 per cent. He had an afebrile and almost asymptomatic hospital stay, being discharged on May 26 with final diagnoses of periarteritis nodosa, uremia, chronic glomerulo-tubular nephritis, secondary anemia, and emaciation.

A letter was received from the patient's physician on March 29, 1939, inquiring about his case, and stating that he was then suffering from nephritis. A subsequent letter stated that he became comatose and died on December 17, 1939, with the death certificate reading "acute uremia, myocarditis, chronic nephritis with hypertension."

Case 11. G. J. A., first admitted on December 27, 1939, is to be reported by Foster.[4] The outstanding features of this case were soreness and tiredness of the leg muscles, diplopia, and blurring of vision. Periarteritis nodosa was suspected and several biopsies showed angiomyositis. Treatment was with sulfanilamide. The patient later had multiple cerebrovascular accidents. Necropsy substantiated the diagnosis of periarteritis nodosa. Positive Kahn reaction reports in this case were considered to be false positives by the dermatology department.

Case 12. A. J. F., a 49-year-old white male, was admitted on January 3, 1940, with a history of having contracted a severe "cold" on July 15, 1939, with rhinitis, malaise, and a cough productive of a small amount of sputum. This condition persisted for two months and was followed by ease of fatigue, mild palpitation, and dyspnea on slight exertion. Four weeks prior to admission, dull pain occurred in both calves and thighs which was made worse by exercise and relieved by rest. He had had fever as high as 102.5°, with night sweats, anorexia, morning headache, weight loss, soreness of arms, and low-back pain. Following exposure to cold, the patient noticed that both hands became blue and then white. A normal color followed immersion of the hands in warm water. He had noticed that for a few weeks his urine had been dark and stained his underwear. One tablet of sulfanilamide had been taken three times daily for two weeks prior to admission. For five or six years he had been troubled with occasional spells of diarrhea at which time he had two or three watery stools daily. There has been no change in this during the present illness. Otherwise, the past history was essentially normal.

Physical examination revealed a well developed, well nourished male, not appearing acutely ill but with a slightly icteric tint to the sclerae. The temperature was 99.6°; pulse, 84 per minute; respiration, 20 per minute; and blood pressure, 108 mm. Hg systolic and 78 mm. diastolic. The nasal mucosa was markedly injected. The heart and lungs were normal. The liver edge was palpable and slightly tender 3 cm. below the right costal margin in the mid-clavicular line. The extremities appeared slightly atrophied with slight tenderness present in the muscles of the calves and thighs. At times there was a splotchy, light blue color of the hands and feet. Otherwise, the examination was essentially normal.

The Kahn reaction was negative. Urinalysis revealed a faint trace of albumin, rare red blood cells, and a few hyalin and finely granular casts. Hemoglobin was 76 per cent and 79 per cent on two occasions. White blood cell counts were normal, with 7 per cent and 3 per cent eosinophilia on two differential counts. The stool examination showed a positive guaiac reaction. Phagocytic index for brucellosis and

typhoid-dysentery-brucella agglutinations were negative. No amebae were found in the stools. The sedimentation index was 0.83 mm. per minute (corrected). Blood bilirubin was 0.5 mg. per cent (indirect). The bromsulphalein liver function test showed 100 per cent retention of the dye in 30 minutes. Trichina antigen skin tests in dilutions of 1 : 10,000, 1 : 500, and 1 : 100 were all positive in 24 hours. Biopsy of the left gastrocnemius muscle was reported "Some of the medium-sized arteries show a marked thickening of their wall with reduction in the lumen. There is a perivascular infiltration of inflammatory cells of various types including an occasional eosinophile. Periarteritis nodosa. No evidence of trichinosis." (Dr. R. C. Wanstrom.) Chest and spine roentgen-rays were normal.

The patient had a daily afternoon fever as high as 100 degrees. Pulse rate averaged 85 per minute. He had few complaints while at bed rest and was discharged on the ninth hospital day, essentially the same as at the time of admission. He was instructed to continue getting much rest.

The patient was seen in the out-patient department on April 9, 1940, with a letter from the outside physician stating that the "jaundice deepened for a period of about three weeks until on January 23 he had a quantitative van den Bergh test of 5.6 mg. per cent. His liver edge at this time was palpable at the level of the umbilicus and moderately tender. . . . By the middle of February his jaundice had entirely disappeared, the liver had receded markedly in size, and he felt much better in every way, complaining of no pain in his extremities even though he was up and about a short time each day." [47] The patient, at the time of this examination, stated that he had improved and had gained eight pounds in weight since discharge. Slight dyspnea was still present and recently he had been troubled with soreness in the heels. The blood pressure at that time was 138 mm. Hg systolic and 85 mm. diastolic. The hands were warm and slightly cyanotic, and feet were cold but pink. The liver edge was 2 cm. below the right costal margin. Blood bilirubin was 0.1 mg. per cent (indirect), and the bromsulphalein test showed less than 10 per cent retention in 30 minutes. Urinalysis was normal except for an occasional red blood cell. Hemoglobin was 95 per cent and white blood count 10,100 with 8 per cent eosinophiles.

The patient returned for another examination July 29 stating that he had improved, having gained 15 pounds in body weight since discharge from the hospital. There continued to be very slight ease of fatigue and dyspnea on exertion and occasional pain in the heels, insteps, and calves of the legs after exertion or walking. This was relieved completely by rest. Otherwise, he was asymptomatic at the time. He stated that in April he had quite severe testicular pain lasting for three days, with no recurrence. Examination at this time showed no abnormalities except a slight splotchiness of the palms of the hands. The blood pressure was 124 mm. Hg systolic and 80 mm. diastolic, and the liver was not palpable. Urinalysis, complete blood count, urea clearance test, and electrocardiogram were all normal.

When last seen on November 4, 1940, the patient was in better condition than he had been in over a year or more, and his body weight was greater than it had ever been before. He had continued to obtain much rest as previously instructed. His only symptoms were occasional minor shooting pains in his arms, heels and soles of his feet. For two days, two weeks prior to being seen, he had had a mild tight sensation in his head, which was similar to that which he had experienced occasionally for several years prior to the onset of the present illness. At this time, the patient recalled that in November, 1939, he had had swelling of his testicles with slight soreness for about a week. Physical examination revealed a healthy looking man with slight nasal congestion. Blood pressure was 148 mm. Hg systolic and 94 mm. diastolic. For the first time the left testicle was noted to be atrophic. The second aortic valve sound was somewhat loud. Otherwise, examination was normal. Urinalysis and blood examinations, including a differential count, were normal at this time except for a

white blood count of 11,900. A biopsy taken near the site of the previous biopsy unfortunately failed to include a fair-sized artery. However, "some of the smaller arteries show a definite thickening of their walls but the inflammatory infiltrations previously seen are largely absent in this specimen." (Dr. R. C. Wanstrom.)

Case 13. L. M. C., admitted on March 12, 1940, is to be reported by Scurry.[5] This patient had the chief complaints of palpitation, fatigue, dyspnea, and fainting of four months' duration. There was also a sensation of constriction or pressure in the chest and one of numbness in the arms when they were in the dependent position. The clinical diagnosis was rheumatic heart disease, but necropsy showed an unexpected pulmonary periarteritis nodosa.

Case 14. H. B., who was admitted on November 4, 1940 and is to be reported by Hamff,[6] had a history of pains in the extremities and headache, the former beginning in July, 1940. For a period of three months, nine years ago, he had experienced a similar but less severe attack of pain in his extremities which was relieved by the extraction of several teeth. Ten days prior to admission the patient had sudden loss of consciousness for half a day. There had also been weakness, weight loss, abdominal pain, and blurring of vision. Blood pressure was 218 mm. Hg systolic and 128 mm. diastolic on admission. Periarteritis nodosa was suspected, but a gastrocnemius biopsy was negative. The patient then had a splanchnicectomy. Biopsy of a left intercostal artery at that time showed periarteritis nodosa.

Addenda

A. J. F., Case 12, was again seen in December, 1941, at which time he had returned to work. He had developed no new symptoms and was feeling well. His blood pressure was normal, 120 mm. Hg systolic and 80 mm. diastolic. Also in December, 1941, a letter was received from the wife of H. B., Case 14, stating that he had returned to work, that his blood pressure was 'normal,' and that he was feeling the best he had felt in 20 years.

The duration of life from onset of illness in Case 12 has, therefore, increased to two and a half years; and the average duration of the cases herein reported has increased to 14 months. The prognosis, at least in a few cases, seems slightly better than predicted previously. Furthermore, results in Cases 12 and 14 seem to substantiate the possibility that some improperly diagnosed cases of periarteritis nodosa may have longer duration of life than present reports indicate.

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ANTICIPATION AND DIAGNOSIS OF NEURO-CIRCULATORY ASTHENIA *

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IN the midst of World War I, when American physicians were widely scattered, meetings of such representative groups as this were unknown. It is likely that many medical officers of the armed Services, absorbed in their various duties, heard little of a condition known to certain of their colleagues as the irritable heart of soldiers, or neuro-circulatory asthenia or, perhaps, the effort syndrome. Some were satisfied with the official terminology D.A.H. (disordered action of the heart). Those who remained in civil posts had little interest in the matter, since the disorder, by and large, is not a peace-time problem. Various stresses and strains of military life form the basis of the typical case.

Credit for the original description of the irritable heart is usually given to DaCosta,[3] who observed the syndrome among soldiers in hospitals toward the end of the American Civil War (1864). It is clear, however, that a number of clinicians were familiar with the condition. It was discussed in meetings of the profession in Philadelphia, where many soldiers, exhausted by the strain of warfare, dysentery, typhoid and other hazards, were languishing in military hospitals. Hartshorne, speaking before the College of Physicians of Philadelphia, June 3, 1863, stated that Alfred Stillé had made the first report. In a Presidential address before the Philadelphia County Medical Society on February 11, 1863, Stillé,[20] referring to the peculiar palpitation of soldiers, spoke as follows: "Its ordinary association with a frequent pulse, or one rendered so by the erect posture, seems to prove it to be an effect of muscular debility of the heart alone, or of that organ along with the rest of the muscular system. It was not attended with any irregularity of the pulse nor, ordinarily, with any distinct murmur in the heart, not even with a soft, blowing murmur, nor was any such observed in the arteries as an ordinary symptom." Stillé considered the condition to be characteristic of army life, in contrast with civilian. Four months later, Hartshorne [6] noted that soldiers with this condition suffered from dyspnea after even moderate exertion, whereas there were no characteristic physical signs, such as cardiac dilatation or hypertrophy; they seemed overcome by army duties. Several months of hospital care only *improved*, never cured, his patients. He considered them unfit for full duty, though suited to light duty of various kinds.

Stillé's address was followed by its publication in 1863. His report, incomplete though it is in some respects, clearly antedates that of DaCosta, whose book was not published until 1864. A review of this book can be found in the American Journal of the Medical Sciences for October, 1864. Hartshorne's address appeared in the same journal in the same year. It is

* Read at the Boston meeting of the American College of Physicians, April 22, 1941.

not clear whether Hartshorne or DaCosta should be given second place in this race for priority, but Stillé was *facile princeps*.

Nevertheless, DaCosta cleared up certain features. He added the description of pain in the lower precordium to Stillé's picture. As etiologic agents, he found fatiguing marches, fever and diarrhea.

When the Office of the Surgeon-General [21] issued the Medical and Surgical History of the War of the Rebellion in 1879, the irritable heart of soldiers was all but forgotten. Among five huge volumes, I could find merely a statement to the effect that of 200 men with irritable heart, DaCosta had found that 61 were suffering from diarrhea or had recently recovered therefrom.

Each designation—neuro-circulatory asthenia,* effort syndrome, and the irritable heart of soldiers—has its advantages. Perhaps the first is the most descriptive of the perverted physiology of the condition. Effort syndrome indicates the precipitating cause and the cause of the disability. The writer prefers the irritable heart of soldiers because of its historic implications and its American origin, its military association, and the central fact of the syndrome which, after all, according to the men involved, concerns itself primarily with certain uncomfortable sensations which they refer to their hearts.

The Condition in Civil Life

Outside military life the syndrome is uncommon. The explanation is simple: the large majority of predisposing and direct causes do not exist in civil life. Physical strain of a person who is not qualified to bear it adequately is perhaps the most frequent precipitating factor. In civil life a man has control over his own efforts, and, if not built to be a professional wrestler, he takes employment as a clerk, florist, or perhaps window-dresser. In the Army, the clerk or window-dresser has little choice of action. However, to make the picture more real, let me cite the following cases from my practice:

Case 1. A white man, aged 34, a radio salesman, had been in previous good health until an attack of typhoid fever in March, 1940. Convalescence was protracted because of "cardiac symptoms," manifested by tachycardia, fatigue on slight exertion, and pain in the lower left chest outside the cardiac apex. For six months he had drawn disability insurance, but this was finally cancelled. In January, 1941, examination showed a healthy-looking man, with a normal cardiovascular apparatus in every respect save a tachycardia (rate 100). He was unable to do as much work as formerly because of the ready fatigue and disagreeable cardiac pounding.

Case 2. A white business man, aged 59, had for one year been conscious of rapid pulse, with rate 80–90. His feet were cold. There was no dyspnea. After eating he suffered a sense of gas about the left lower rib border with some heartburn, relieved by soda. The tachycardia and the gas seemed to be related. He had finally become prostrated by carrying two suitcases upstairs. He had no actual dyspnea or pain other than the "gas." His cardiovascular apparatus showed nothing whatever abnormal, though his pulse rate was between 96 and 100 per minute.

* This terminology is now used in the new Standard Classified Nomenclature of Disease.

Some time later I was consulted by this patient's clergyman who told me that the patient was very unstable and at certain intervals, roughly every two years, he passed through phases when he became disagreeable, felt that people were treating him badly or insulting him. These phases would pass off spontaneously, probably being recurring depressions.

Neither of these patients has had rheumatic fever, and there was no reason to suspect organic disease in either, save the possible effect of the typhoid fever in the first one. They were both instances of the irritable heart, and represent important etiologic factors: first, infection, and the lure of capitalizing on the condition in case 1; and second, the unstable or emotionally sensitive background of some patients as shown in case 2. In civil life these men were able to adapt their work to their handicap. In the Army they would doubtless both have become casualties.

The Present Problem

In the year 1916 the British military heart hospital treated 558 cases of the effort syndrome.[11] In a similar period over 300 cases passed through U. S. General Hospital No. 9 at Lakewood, N. J. About four-fifths of the British cases were drawn from France, whereas a larger proportion of American patients had not seen actual combat.

Now that Selective Service is upon us, it is clearly our duty to be cognizant of this syndrome and to prevent, so far as possible, the acceptance of potential cases into the armed forces. In this effort the internist and the psychiatrist must work together. Some cases will occur despite our care. The scope of the casualties will depend further upon several contingencies—the rapidity with which the troops must be trained; the prevalence of such infections as influenza, pneumonia, and dysentery; the length of convalescence permitted from such infections; and whether the troops see actual combat.

Predisposing Factors

It is very difficult to predict who will break under the effects of infections, but there is general agreement that certain types of recruits are predisposed, physically or mentally, to the syndrome. At Lakewood, with the help of Campbell,[2] certain categories were recognized. One group consists of the *constitutionally inferior:* such men may be physically defective but mentally competent; mentally defective but physically adequate; or defective in both departments. Another is the group of *chronic invalids:* such men have suffered from cardiac symptoms for years, despite the absence of demonstrable heart disease. The importance of this group was emphasized by Friedlander and Freyhof.[4] Some such men have had rheumatic fever and may have an actual myocardial defect, but many give a history of pure cardiac neurosis. Such are the men who, for some obscure reason, develop cardiac symptoms under mental or physical strain, whereas others develop indigestion, headache, or some other disorder. There is also the group which was designated at

Lakewood as the *emotionally sensitive*. Some break down following harrowing experiences, such as burial, intense bombardment, and the sight of mangled comrades. For example, a man may drive himself to stand up under gunfire, but he can not control the trembling of his legs, the sweating, and the palpitation of his heart. The conflict between a natural desire to run from the scene of battle and the subconscious lure of life in a hospital behind the lines on one hand, and the man's desire to do his duty on the other, is a debilitating one.

Symptoms

Once established, the picture is characteristic, regardless of etiology. The man is *lackadaisical* because of the discomfort encountered on moving about. He may complain of cold even in moderate temperature, and may "hug" the stove. He may be prostrated by walking the length of a room. *Fatigue* is real and measurable, and not imaginary (King).[7] *Sweat* may roll from the axillae, especially on exertion or during examination. *Tremor* is common and may be disturbing to the subject. *Giddiness* is common. On exertion or during excitement the *pulse rises*, the *heart pounds*, and *breathlessness* is experienced. *Precordial pain* is common. Though it has been reported as occasionally being referred to the left arm, the writer has not noted this. The typical pain is not so oppressive or so inspiring of dread as is true angina; rather, one derives the impression that it is more in the nature of a "stitch in the side," and is typically located in the lower precordium in the region of the cardiac apex. The extremities may be flushed and even cyanotic; are frequently cold and clammy. *Dermatographia* has been noted in a certain group.[14] The writer does not recall this last symptom as a common finding since the normal white tâche seen on stroking the skin with a blunt instrument was found in the Lakewood tests with considerable regularity.

Signs

The patient may be of vigorous appearance, since the unstable and the undeveloped personality is no respecter of physique. A general constitutional inferiority, with emphasis on lack of physical development, may be recognizable at a glance.

Outside the "typus" of the man and the evidences of breathlessness and fatigue and a certain overactivity of the circulatory apparatus, there is little to distinguish the man with irritable heart. The writer,[8] during World War I, recorded the auscultatory findings in 500 men who were doing regular army duty. Every peculiarity encountered in the examination of the man with irritable heart could be matched by frequent findings of similar peculiarities among normal men. True, the "overactive" heart stirs up rather often a cardio-respiratory murmur in the adjacent lung. Systolic murmurs over the pulmonary conus, and at the apex in the recumbent posture, are common, but they are physiologic and are in no way characteristic of the irritable heart.

The pulse is labile, being rapid under exertion or excitement, but almost invariably it can be found below 90 per minute after rest. Lewis [10] gives the average figure as 85.

Muscular strength is frequently below par. Smith [16] noted defective strength in certain muscle groups, at times a general lack of strength. This was demonstrated at Lakewood by means of the spring balance, and records of progress in strength under graded exercise could be made.

It is a medical commonplace, verified frequently in World War I, that the man with a long thin chest is likely to lack endurance. In Civil War days, Hartshorne [6] noted that the cardiac impulse of men with soldier's heart was "sudden, a little less in force than normal." In a most careful teleroentgenographic study in World War I, Smith [17, 18] found that the hearts of 69 men with irritable heart could be differentiated, as regards size, into two groups—those with cardiac symptoms of long standing, and those who acquired symptoms during Army service. In the former group, the hearts were somewhat smaller than normal, whereas measurements in men who acquired symptoms in the Army were similar to those of normal "control" subjects.

Extending such observations, Starr et al.[19] have shown that persons who have symptoms of neuro-circulatory asthenia in peace-time not only show small hearts, but also diminished average cardiac output, stroke volume, and total cardiac work per minute.

The observations of Smith and of Starr and his associates are, then, in agreement as regards the reduced size of the heart in the individual who is liable to irritable heart either in peace-time or in military service. However, there remains a group in whom the heart is of normal size who break from the effects of war; such are the cases that follow infections, or the effects of actual gunfire, horrifying experiences or other forms of exposure to combat conditions.

Diagnosis

Recognition of irritable heart is based largely on the symptoms and signs noted above. The syndrome is more or less uniform, but the background of the patients is so varied that each case must be studied individually.

Differentiation of the types of *chronic invalidism, intelligence defect,* and *emotional sensitivity* can be made only through a most careful anamnesis. The *physically defective* type may be recognized on inspection, or through exercise tests. The *post-infection* type gives a characteristic history.

The resemblance between this condition and hyperthyroid states is merely superficial. After one-half hour's rest, the pulse in irritable heart usually finds a level below 90 per minute, whereas in hyperthyroid states it usually exceeds 90. The basal metabolic rate in irritable heart is not elevated; on the contrary, it is frequently below the average figure, especially in the asthenic individual. The epinephrine test may be expected to prove positive in 60 per cent of men with irritable heart.[24] The reaction is rather leisurely,

beginning after an average lag of 12 minutes, and reaching a peak in 32 minutes. This contrasts with the reactions found by Goetsch [5] in hyperthyroid states, which occurred "early," and with the reactions encountered in women at the menopause by Myers and King [13] in which the reaction reached its peak in an average of eight minutes.

Tuberculosis may present a superficial resemblance to the irritable heart; by careless examination either condition may be mistaken for the other. However, the writer [9] has shown that the relation between the two disorders is no more than coincidental.

Finally, some form of exercise test, with observation of the pulse reaction and degree of breathlessness and fatigue induced is essential to the diagnosis. American observers [14] with Lewis in World War I found the simple test proposed by Meakins and Gunson [12] to be satisfactory. This test consists of putting the subject through 75 paces at an ordinary brisk walk, followed by walking up 27 steps (18 feet). If the pulse rate fails to return to its previous level in two minutes after the test, the man's endurance is presumed to be impaired, and he will probably prove unfit for full duty. It was pointed out, however, that this rule deserves some latitude in application.

The Perverted Physiology

The symptoms concerned with this syndrome can be produced by a variety of stimuli, mental and physical. The results are much the same whether the man has built up a conditioned reflex to the sound of gunfire, is sent to duty too soon after influenza, or is an asthenic or constitutionally inferior individual unfit for service. In a majority of instances the syndrome may be reproduced by the injection of epinephrine, whereas no reaction is observed in healthy subjects. Since epinephrine acts on the sympathetic nerve-endings, it may be deduced that the sympathetic system in many such men is exceptionally sensitive, or at least unstable. Further evidence of vasomotor asthenia is the inability of patients with this syndrome to maintain the white vasomotor tâche, produced by stroking the skin with a blunt instrument, as long as do normal men.

In military life the probable cause of many cases is emotion, causing an outpouring of epinephrine into the blood stream; the sensitive sympathetic nervous system is stimulated, with the production of the symptoms previously noted. In other words, the man is sensitive to his own epinephrine. A similar sensitiveness or instability may be caused by certain infections, whereas in other cases it is probably congenital and inherent in a constitutional inferiority.

The Prospect

The condition is not likely to reach serious proportions unless our Army enters combat conditions, though unwise training and infectious diseases not thoroughly compensated for by adequate convalescence may precipitate cases

at any time. In an attempt to "harden" troops by forced marches and lack of proper food and rest, men who might develop into good soldiers by gradual physical training may be broken. It is also important to observe the effect of serious illness in individual cases, and, if indicated, arrange a course of gradual physical rehabilitation. In any case, however, the purpose of an Army is to be prepared for war, and toward that end the present Army must be recruited. I am informed by the Office of the Surgeon-General that "mild" neuro-circulatory asthenia is no bar to acceptance into the Army; if the condition goes beyond this degree the man is rejected altogether. I am inclined to agree with this rule in principle, though it would seem wise to be rather careful in its application. A man may show a somewhat labile blood pressure and pulse under the excitement of being examined, yet his history may show that he is an "All-American" athlete. Such a man recently volunteered and was rejected. On the other hand, a man with similar findings may have been a chronic invalid, unaccustomed to exercise because it disagreed with him. In my opinion the athlete should have been accepted, but we shall indulge in hope versus experience if we induct the chronic invalid. If the recruit is clearly of one of the types likely to develop the syndrome of irritable heart, he should be rejected (i.e., placed in Class 4 as ordered by the Surgeon-General) unless the demand for man-power becomes such as to require the establishment of "limited duty" classes in the Army. It should be kept constantly in mind that the recruit is more than a neuro-muscular-circulatory mechanism; he must be considered as a *person* by authorities who wish to estimate his aptitude for military service.

Conclusions

Recognition of a potential case of irritable heart is the joint responsibility of the psychiatrist and the internist. The former must ask the internist whether the recruit's history and symptoms are explainable on physiologic grounds; the internist should enquire whether they result from defects of intelligence, emotion, or environment.

The psychiatrist should be expected to recognize potential cases based on:

A. Intelligence defects.
B. Unstable reaction to authority (parental, clerical, etc.).
C. Chronic invalidism, especially referred to the cardiovascular system.
D. Emotional instability; sense of inferiority resulting from sex maladjustment, fear of warfare, fear of shirking, etc.

The internist should eliminate men with symptoms based on the following backgrounds:

A. Recent infections.
B. General physical (constitutional) inferiority.
C. Cases with demonstrably small hearts.
D. Asthenic habitus (with "ventral" heart).

E. Neuro-circulatory sensitiveness (history of abnormal reaction to coffee, tobacco, and alcohol may afford a clue).

Special Tests. Some form of exercise test is essential. That suggested by Meakins and Gunson (v.s.) seems as good as any.

In doubtful cases it would be very desirable to apply the epinephrine test. A positive response to injection of 0.5 c.c. of 1 : 1000 solution consists of a rise of blood pressure of 10 mm. or more, a rise in pulse rate of 10 or more beats per minute, with tremor, nervousness, palpitation of the heart, sweating, and so on. Men with positive reactions were found unfit for duty by Wearn and Sturgis [24]; such men should be rejected today. A negative response does not eliminate the diagnosis, since, although 60 per cent of men with irritable heart gave a positive reaction, 40 per cent with similar symptoms failed to respond. The positive epinephrine test is merely additional evidence that the subject is poor material for military service.

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THE CLINICAL MANIFESTATIONS AND DIAGNOSIS OF CHRONIC BRUCELLOSIS *

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In a private practice which included a large group of patients with chronic complaints an appreciable number gave stories strongly suggestive of chronic brucellosis. Agglutination tests sent to the state laboratory were consistently negative. The problem, then, was the correct recognition of a disease which, in its chronic form, exhibits protean but ill-defined manifestations, and the correlation of these varied clinical aspects.

That brucellosis exists as a chronic, protracted disease, in addition to the acute self-limited form, has been recognized by Hardy,[1] Huddleson,[2] Evans,[3] Calder,[4] Cameron and Wells,[5] and others.

Evans [3] recognized the unreliability of the accepted laboratory procedures for its detection. In a group of 28 chronic cases diagnosed clinically, the organism was recovered from the blood in but seven cases; 46 per cent gave negative agglutinations, or titers of less than 1 : 40 dilution, and in 39.3 per cent the intradermal test with brucellergen was negative. However, in 14 cases who had recovered completely the skin test was positive in 92 per cent.

Gould and Huddleson [6] regarded the intradermal test with brucellergen as a reliable indicator of brucella infection. They believed that if the test was negative, brucellosis could usually be ruled out. A positive test, however, does not indicate clinically active infection. Menefee and Poston [7] obtained a 10 per cent incidence of positive tests in a group of healthy students none of whom gave a history of active brucellosis. Meyer [8] and Kolmer [9] found that previous vaccine injections did not induce positive intradermal reactions. A positive reaction, therefore, can be regarded as having the same significance as a positive tuberculin in tuberculosis.[10] It indicates past or present brucella infection but bears no relationship to clinical activity.

The test may be done with brucellergen as developed by Huddleson,[2] or with a suspension of heat killed organisms. Keller [11] and Angle [12] found brucellergen and a heat killed vaccine of *B. suis* and *B. abortus* † equally effective, although the latter gave a higher incidence of local sloughs and systemic reactions.

The agglutination test may be positive, in dilutions of 1 : 40 or more, without any evidence of clinically active brucellosis.[2, 7] In the chronic cases it remains negative in a much higher percentage than in the acute form.[3]

Evans [3] found the opsonocytophagic index the least reliable of the laboratory methods. Thus, it is clear that no single laboratory procedure can be relied upon as an indicator of active chronic brucellosis. Recognition of

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† Prepared by Jensen Salsbery Laboratories Inc., Kansas City, Missouri.

chronic cases remains a clinical problem using the laboratory procedures available as aids rather than as determining factors.

Although recognizing the limitations of the intradermal test, it was felt that a comparative analysis of the positive and negative reactors in a group of patients with chronic complaints should reveal significant data on the varied clinical aspects of chronic brucellosis. Furthermore, information of value in differential diagnosis should be obtained. Therefore, 100 ambulatory patients with chronic complaints were skin tested and thoroughly studied clinically.

Tests were all done intradermally with .04 c.c. heat killed antigen of *B. suis* and *B. abortus,** the same antigen used by Keller [11] and Angle.[12] They were read on the fourth days. A red indurated papule 5–10 mm. in diameter was regarded as 1 plus, an area 10–15 mm. in diameter as 2 plus, an area 15 mm. or over as 3 plus, and a local slough as 4 plus. Sedimentation rates were done by the Westergren technic. Satisfactory blood cultures and opsonocytophagic technics were not available. The cases with cholelithiasis or peptic ulcer were confirmed by roentgen-ray.

The patients were drawn from a town and rural group in Ohio. Approximately 50 per cent used raw milk regularly from their own or neighboring herds. All had been exposed to raw milk in the past and a few were in direct contact with pigs as well as cows.

A comparative study of the skin test positive and negative groups is presented in chart 1 with analysis of the major presenting signs and symptoms. The term recurrent "grippe" is retained because it was invariably used by the patients in relating their histories to describe recurrent attacks of prostration, fever and malaise, with or without associated upper respiratory infection or rheumatism.

Thirty-eight per cent had positive skin tests, whereas in 62 per cent the reaction was negative. Chronic low-grade fever, headache, recurrent "grippe," night sweats, colds, angina pectoris, dyspnea, joint and muscle pains were noted much more frequently in the skin test positive than in the skin test negative group. Palpitation, chronic exhaustion, easy fatigability, nervousness and gastrointestinal complaints occurred with equal frequency in both groups.

Table 1 shows the distribution and grouping of pertinent symptoms and signs among the patients of the skin test positive group.

"Grippe." Eleven patients, or 29 per cent, of the positive reactors gave a history of recurrent "grippe" in contrast to an incidence of 8 per cent in the negative group. Cases 29 and 34 had typical attacks of clinical influenza similar to those encountered in the negative reactors. The remainder, however, described a rather characteristic clinical syndrome. It began with insidious prodromata of increasing exhaustion and joint manifestations or the onset was abrupt. The acute phase was characterized by chilliness or chills, prostration, malaise, headache, backache, fever, anorexia, sweating,

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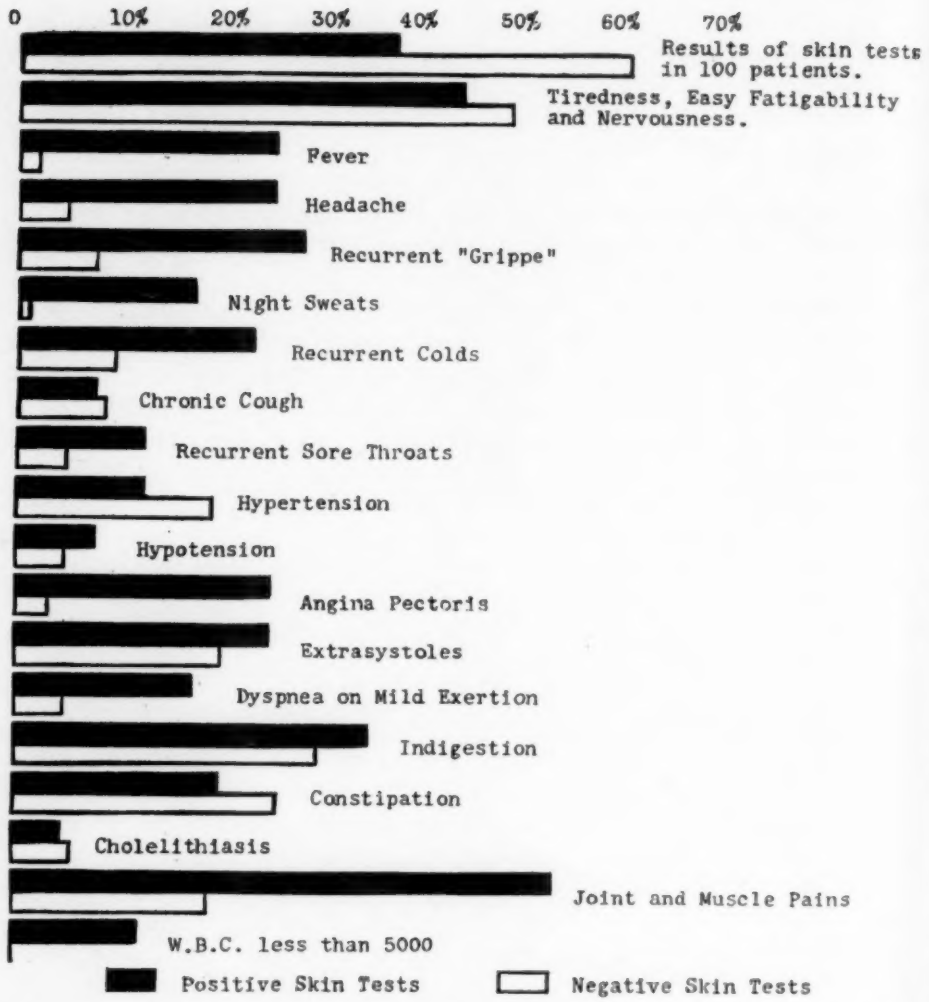

CHART I. A comparative analysis of the major symptoms and signs observed in the skin test positive and negative groups.

night sweats and sometimes gastrointestinal complaints, all merging into a prolonged period of convalescence. Joint manifestations and muscle soreness appeared in the prodromal period but more frequently in the acute or the convalescent phases. When present, upper respiratory complaints of rhinorrhea, cough or sore throat occurred most commonly several days after onset of the illness. Certain aspects suggest an attack of influenza. The long continued fever and other associated complaints, in the absence of focal complications such as sinusitis, are more compatible, however, with a recrudescence of brucellosis. Cough and upper respiratory manifestations are not unusual in chronic brucellosis.[1, 3] Bogart,[13] Beatty,[14] and Lafferty and Phillips [15] have described roentgenological changes in the lungs consisting of

increase in the hilar root shadows and peribronchial infiltration. Carpenter [16] has recovered the brucella organism from tonsillar tissue. Consequently, the associated upper respiratory manifestations are compatible with a recrudescence of brucellosis.

Coronary Disease. The incidence of coronary artery disease is of particular interest as it has not been described previously as a feature of brucella infection. It occurred in 26 per cent of the skin test positive group in contrast to only 3.5 per cent in the negative reactors, although hypertension predominated in the latter group.

The associated pertinent symptoms have been listed in table 1. Additional information is summarized in table 2. The average age of onset for the group was 46.1 years with an average duration of symptoms of 6.5 years. In four, symptoms appeared in the third decade of life. None had valvular

TABLE I

The Distribution of the Pertinent Signs and Symptoms Found in the Patients with Positive Intradermal Tests

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Sex	M	M	M	F	F	F	F	F	F	M	M	M	M	M	M	F	M	M	F
Age	40	38	32	45	28	53	34	37	63	29	52	33	58	55	24	45	21	72	42
Skin Test	xxxx	xx	xxx	xxxx	x	xxxx	xxxx	x	xx	xxx	xxxx	xxxx	xxxx	xxx	xxx	xx	xx	xxx	x
Chronic fatigue and nervousness	x			x	x	x		x		x	x		x			x			x
Temperature				x	x	x	x			x							x	x	
Headache	x			x	x	x	x	x		x					x				
Recurrent "grippe"				x	x	x		x		x								x	x
Night sweats	x			x	x	x	x			x								x	
Colds				x	x													x	x
Cough				x															
Sore throats																			x
Angina pectoris	x	x	x			x												x	
Coronary occlusion	x																	x	
Indigestion	x				x	x		x		x	x		x		x	x		x	x
Constipation	x				x					x			x		x	x		x	
Joint and muscle pains	x			x		x	x	x	x	x	x		x		x	x	x	x	x
Sedimentation rate mm. per hr.	4	4	6	8	14	15		7	30	3	7		24			9	3		4
White blood count	7,300	9,800	4,700	6,800	4,600	7,900	10,700	9,100	6,000	10,500	6,300	5,700	9,100	4,300	5,900	5,500	4,500	5,900	8,300
Polys.			50	69		60	69	63		54	62	53	58	65	42	49	66	63	72
Lymphs.			39	26		32	26	29		41	26	34	30	27	47	39	27	37	23
Roentgen-ray of chest for TBC	neg.			neg.	neg.	neg.	neg.			neg.			neg.				neg.		
Systemic reaction to skin test				x		x	x					x							

TABLE I (*Continued*)

Case	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Sex	M	M	F	M	F	M	M	M	F	M	F	M	M	F	M	F	F	F	F
Age	25	39	46	45	50	67	64	33	64	14	46	47	67	54	11	14	7	20	44
Skin test	xxxx	x	xx	xx	xxxx	xxx	xxxx	xxxx	xxxx	xx	x	xx	xxx	xxx	xxxx	xxxx	xx	x	xxx
Chronic fatigue and nervousness	x		x	x	x		x				x			x		x			x
Temperature			x													x			x
Headache				x										x					
Recurrent "grippe"										x		x					x		x
Night sweats																			x
Colds	x	x								x						x	x		x
Cough																	x	x	x
Sore throats		x								x						x			x
Angina pectoris		x				x	x						x						x
Coronary occlusion													x						x
Indigestion	x		x	x									x	x					x
Constipation																			
Joint and muscle pains	x			x	x	x			x		x	x	x			x			
Sedimentation rate mm. per hr.	3	9		7	5	13	10		11		10	6	7	7		10			6
White blood count	12,000	9,200	7,600	8,350	7,900	8,500	10,800	6,200	8,600		7,200	7,600	7,000	8,150	7,900	12,900	9,800		4,050
Polys.	54	77	64	60	62	65		70	66		78			45	69	56	43		60
Lymphs.	35	16	25	34	32	21		28	32		20			47	26	37	41		30
Roentgen-ray of chest for TBC			neg.	neg.							neg.	neg.				neg.		?	neg.
Systemic reaction to skin test								x	x										x

TABLE II

Coronary Artery Disease in the Group with Positive Intradermal Tests

Case	Sex	Skin Test	Age Onset Coronary Disease	Present Age	Duration in Yrs.	Blood Pressure	Valvular Disease	Coronary Occlusion
1	Male	xxxx	32	46	8	140/78	No	Yes
2	Male	xx	37	38	1	120/70	No	
3	Male	xxx	31	34	1	135/85	No	
6	Female	xxxx	41	53	12	150/90	No	
18	Male	xxx	52	72	20	124/70	No	Yes
21	Male	x	36	39	3	160/100	No	
25	Male	xxx	63	67	4	150/85	No	
26	Male	xxx	57	67	10	175/110	No	
32	Male	xxx	59	64	5	130/78	No	Yes
38	Female	xxxx	43	44	1	125/75	No	Yes

disease, such as aortic stenosis, to account for the anginal symptoms. The two patients in the skin test negative group had onset of symptoms at the age of 58 and 61 years with blood pressures of 170 mm. of Hg systolic and 90 diastolic and 180 mm. systolic and 105 diastolic respectively.

A clinical diagnosis of chronic brucellosis was made in four of the positive reactors (cases 1, 6, 18 and 38).

The onset of angina in case 6, at the age of 41, followed an acute exacerbation of her chronic illness, which strongly suggests a causal relationship between the two. She had a temporal arteritis in one attack. This raises the question of a similar lesion in the coronary arteries as the underlying cause of her angina pectoris.

Horton and Magath [17] have described temporal arteritis of unknown etiology with low-grade fever, malaise, headache and anemia in a group predominantly of farm women. One had involvement of the radial artery but none had coronary disease or joint manifestations. Agglutinations for brucellosis and cultures were negative. The clinical histories are not sufficiently suggestive to warrant a clinical diagnosis of brucellosis.

Eyre [18] noted that the endothelium of the blood vessels was damaged so that blood easily passed through and localized extravasations of blood were frequently encountered in acute melitensis infections. However, no definite evidence of arteritis has been reported.

Case 38 developed symptoms of coronary disease at the age of 43 although her blood pressure had always been normal or low. The rarity of coronary disease in a woman of this age group without hypertension or other apparent cause makes the relationship to her brucellosis an interesting speculation.

Cases 1 and 18 both had long histories of chronic brucellosis. Case 1, a farmer all his life, had had symptoms between the ages of 14 and 18 years, recurring again around the age of 28 and continuing irregularly. Typical anginal attacks related to exertion and relieved by nitroglycerine and rest had recurred since the age of 32. When 43, he had had a severe attack of substernal pain, lasting "half the night," treated by his physician as coronary occlusion. Case 18 had anginal attacks which began at the age of 55. He had had recurrent symptoms of chronic brucellosis since the age of 25.

The age of onset of angina in cases 2, 3, and 21, at 37, 31 and 36 years respectively, is of interest. None of these patients had any other symptoms suggesting brucellosis.

Palpitation and extrasystoles were frequent complaints. No other cardiac manifestations were encountered with sufficient frequency to be considered significant.

Rheumatism. Rheumatic manifestations were found in 55 per cent of the skin test positive group in contrast to 20 per cent in those with negative reactions.

The rheumatic complaints in the positive reactors are summarized in table 3. A large percentage showed widespread manifestations most frequently involving the small joints of the hands, the wrists, the lumbar region of the back, and the knees. A few complained primarily of arthralgias but the majority had definite stiffness along with the pain. Local swelling was fre-

TABLE III

The Distribution and Character of the Rheumatic Manifestations in the Group with Positive Intradermal Tests

Case	Sex	Age	Skin Test	Sedimentation Rate mm. per hr.	Muscles	Hands	Wrists	Elbows	Shoulders	Back	Hips	Knees	Ankles	Feet	Manifestations
1	M	40	Slough xxxx	4	x	x	x			xxxx	xx	xx			Stiffness, aching, soreness, lumbago, sciatica.
4	F	45	Slough xxxx	8	x	x	x			xxxx	xx	xx			Stiffness, aching, soreness, lumbago, swelling.
6	F	53	Slough xxxx	15	xx	xxx	xx	x	x	xxx		xx	xx	x	Stiffness, aching, soreness, swelling.
7	F	34	Slough xxxx	14								xxxx			Recurrent swelling 3–4 week intervals.
8	F	37	x	7		x	x		x	xx		xx			Stiffness, aching, soreness.
9	F	63	xx	30		x						xxx			Pain and soreness.
11	M	52	Slough xxxx	7	x	x	x		x	xxxx	x	xx	xx		Stiffness, soreness, lumbago, sciatica.
13	M	58	Slough xxxx	24	x	x	x	x	x	xxxx	xx	x			Stiffness, aching, soreness, lumbago.
15	M	24	xxx		xx										Sore tender muscles around shoulders.
16	F	45	xx	9		x	x			xxx		xx	x		Stiffness, aching, soreness.
17	M	21	xx	3	xx							x			Sore aching muscles—legs.
18	M	72	xxx			x			x	xxx		xx			Soreness, aching, stiffness.
19	F	42	x	4		xxx	x	xx	x						Stiffness, soreness, swelling, deformity.
20	M	25	Slough xxxx	3				x	x	xxx		x			Stiffness, aching.
23	M	45	xx	7.5	x	x	x	x	x	x	x	x	x	x	Stiffness, aching, soreness.
24	M	50	Gland xxxx	5	x							x			Localized tenderness, fibulo-tibial joint knee.
25	M	67	xxx	13	x	x	x		x	x		x	x		Attack confined him to bed 6 months. No residuals.
28	F	64	Slough xxxx	11					xx	xx					Stiffness, aching, soreness.
31	F	47	xx	6								xx	x		Soreness, swelling.
32	M	67	xxx	7					x						Aching, soreness, limited motion.
33	F	54	xxx	7		x	x	x	x	xxx	x	x	x	x	Stiffness, soreness, in bed 3 attacks.
35	F	14	Slough xxxx	10	x	x	x	x	x	x	x	x	x	x	Migratory pain and stiffness.

quently noted but redness of the joint was not encountered. Eleven patients complained of muscle soreness.

Only one patient (case 19) showed joint deformities compatible with established rheumatoid arthritis. Her sedimentation rate was 4 mm. per hour although the arthritic process was moderately active. None of the others, despite recurrent attacks or long continued manifestations, showed residual deformity or permanent loss of function.

Roentgen-rays in case 19 were compatible with rheumatoid arthritis. The others, with the exception of case 4, revealed nothing more than the hypertrophic changes compatible with their age. Case 4 showed extensive scattered areas of miliary calcification in the left gluteal muscles which were considered to be due to myositis ossificans.

The striking laboratory feature of the group was the normal sedimentation rate in all except one (case 9), in spite of active joint manifestations, and, in some, of concomitant fever. In contrast, seven patients in the skin test negative group, who showed evidence of joint disease compatible with active rheumatoid arthritis, had sedimentation rates ranging from 24 to 68 mm. per hour. Both groups complained of increased joint manifestations during the fall and winter months and after exposure to cold. In patients with other symptoms consistent with brucellosis the relationship of the joint manifestations to chronic brucella infection is quite definite. Those with joint symptoms as a more isolated complaint are more difficult to evaluate. The evidence would indicate, however, that chronic cases may exhibit little more than joint complaints of the character described.

Goldfain [19] studied the incidence of brucellosis in a group of patients with rheumatic complaints, most of whom used raw milk. Thirty-one of 50 were diagnosed as having active brucellosis entirely on the basis of laboratory procedures. The rheumatic diagnoses in these 31 cases were atrophic arthritis in nine, or 29 per cent; hypertrophic arthritis in five; ankylosing spondylitis in one; and chronic fibrositis in seven.

The 29 per cent incidence of rheumatoid arthritis would indicate a relationship between rheumatoid arthritis and brucellosis which is not confirmed in the data presented. Therefore, 48 cases of characteristic, well developed rheumatoid arthritis were studied at the Peter Bent Brigham and the Massachusetts General Hospitals, Boston, Massachusetts. This group showed a 13 per cent incidence of positive skin reactions. Furthermore, 175 other patients entering the Peter Bent Brigham Hospital were skin tested to determine the expected incidence of positive reactions. Eleven per cent gave positive tests. The close agreement between the two groups indicates that brucella infection does not play any significant etiologic rôle in rheumatoid arthritis. Sedimentation rates were elevated above normal in all the cases of rheumatoid arthritis tested.

These results are in agreement with Green and Freyberg [20] who found no evidence of brucellosis in 25 cases of typical rheumatoid arthritis. Of 25 patients with joint symptoms and manifestations not compatible "with any

of the common arthritides," three had "quite convincing evidence of active brucellosis" and six others had possible brucellosis.

Invariably, both *headache,* and *chronic fatigue* and nervousness were accentuated during the "grippe"-like attacks and the subsequent convalescence in the positive reactors. Except for this, there were no differences in the character of these complaints in the positive and negative groups. The incidence of migraine was almost identical in both groups. Cases 1, 4 and 7 (positive reactors) had migraine. Attacks were more frequent in periods of ill health but no other relationship was noted.

Gastrointestinal complaints were similar in both groups. Three patients in the skin test positive group had peptic ulcer. It is of interest that two of them had used raw milk and cream on prolonged Sippy régimes while the only patient with peptic ulcer in the skin test negative group had used little raw milk. Harris [21] has commented on the occurrence of peptic ulcer in brucellosis patients. Heavy exposure to raw milk and cream on Sippy régimes may be the responsible factor.

"Protracted fevers" ranged from 99.2° F. to a little over 100° F. The fever reached its peak in the afternoon and was usually normal or only slightly elevated in the morning. Physical and mental strain was apt to result in higher afternoon temperatures.

The *white count* showed some tendency to leukopenia in the positive skin test group. Five had white counts below 5000, whereas none of the negative reactors was below that level. Otherwise, the range was the same in both groups. Two of the 13 cases diagnosed clinically as chronic brucellosis had white counts below 5000. The remainder varied from normal to a moderate leukocytosis.

Table 1 shows the *skin test reaction* in relation to the patients' symptoms. There is no consistent correlation between the two. Local sloughs were encountered in 42 per cent. An appreciable number had associated lymphangitis and axillary adenitis lasting a few days. Local ulcers healed in the course of seven to 21 days. Systemic reactions with fever from 100° F. to 102° F., malaise, prostration and headache were encountered in seven cases. In cases 28 and 38 a moderate systemic reaction lasted from 10 to 14 days. Case 38 had a moderate accentuation of her angina pectoris indicating that caution should be used in skin testing such cases. Cases 12 and 27 had local sloughs and systemic reactions, although neither ever had any symptoms compatible with brucellosis. Dustin [22] has considered a febrile response to antigen as one of several tests of clinical activity. Such an assumption is unjustified and the skin test reaction can not be considered as an index of clinical activity. One patient in the negative group presented a clinical picture compatible with chronic brucellosis. With this exception, the intradermal test was an accurate indicator of brucella infection.

The data presented indicate that the more common manifestations in chronic brucellosis are chronic fatigue and nervousness, protracted low-grade fever, recurrent "grippe"-like attacks characteristically with prolonged con-

valescence, night sweats, palpitation, gastrointestinal symptoms and joint and muscle complaints. Coronary artery disease may be a part of the clinical picture.

The clinical combinations which were encountered most frequently are presented by reviewing representative case histories.

Case Reports

Case 6. This female, aged 53 years, had spent her life on a farm, had milked the cows when able, and had regularly used raw milk from a herd found to be heavily infected. She complained of rheumatism, exhaustion, nervousness and substernal pain on exertion.

Her ill health began at the age of 16 with an attack of rheumatism, which confined her to bed for about three months. "More or less rheumatism" had persisted since then, worse in the winter and on damp days. Joint manifestations consisted of pain and stiffness, most frequently involving the small joints of the hands, wrists, elbows, shoulders, back, knees and ankles. Moderate swelling occurred but never any redness or permanent loss of function. Muscle soreness often accompanied the rheumatism. The pectoral muscles were prone to soreness after hard work and the patient suffered from recurrent "lumbago."

"Grippe" had recurred irregularly since childhood, as often as several times a year in summer or winter, particularly if she overworked. The onset was insidious with increasing joint manifestations and exhaustion; or, at other times, more abrupt. The acute phase was characterized by chilliness or chills, generalized aching and soreness, prostration, fever, night sweats, headache, backache, increased joint stiffness, and often moderate swelling particularly of knees or ankles. Rhinorrhea, cough and sore throat often appeared on the second to fourth day of the attack. The acute phase gradually improved in from 7 to 10 days, merging into a prolonged convalescence which lasted from two or three weeks up to several months. This consisted of low-grade fever, exhaustion, night sweats, headaches and joint manifestations, all of which gradually improved. A severe attack at the age of 41 confined her to bed for 12 weeks. Her physician, at that time, stated that her heart was affected and limited activity was prescribed for another three months. Since then she had complained of dyspnea and of a tight clutching feeling in the substernal area precipitated by exertion and relieved by rest.

Long standing symptoms of nervousness, tiredness and easy fatigability became worse as she grew older. Epigastric gas and fullness after meals appeared. The bowels were always regular.

For several months before she was first seen exhaustion, nervousness and rheumatism had grown worse; epigastric gas and fullness had increased; appetite had become poor; and she was unable to do her own housework.

Physical Examination. Temperature 99.4° F., pulse 82, blood pressure 150 mm. of Hg systolic and 90 mm. diastolic. She was rather obese and was well preserved in spite of the long history of ill health. The knees, ankles, right elbow, wrists and small joints of the hands were painful and stiff on motion. Both knees were puffy. The distal joints of the fingers showed small Heberden's nodes. No A–V nicking was noted in the ocular fundi. The teeth and tonsils had been removed. Thyroid was small. No general adenopathy was noted. The lungs were clear. The heart was somewhat enlarged; sounds were regular and of good quality; no murmurs were heard. Abdominal examination was negative. The spleen was not palpable. Pelvic and rectal examinations were negative.

Laboratory Findings. Hemoglobin 98 per cent, red blood cells 5,190,000, white blood cells 7900, polymorphonuclears 68 per cent, lymphocytes 32 per cent, mononuclears

4 per cent, eosinophiles 2 per cent. Urine revealed a trace of albumin. Kahn and Kline tests were negative. The electrocardiogram was within normal limits. There was no axis deviation. A six-foot film showed a transverse cardiac diameter of 15.5 cm., with chest measurement of 29.5 cm. Sedimentation rate was 15 mm. in one hour. Brucella agglutination was reported negative by the state laboratory. Cholecystograms and sinus roentgen-rays done later were negative. Roentgenograms of knees showed hypertrophic changes compatible with age.

Course. After 10 days of increasing symptoms the patient had abrupt onset of chills with temperature to 103° F. Severe generalized aching and soreness, backache, nausea and vomiting developed. A reddened, indurated, erysipelas-like area appeared over the nose and cheeks in butterfly distribution. Both knee joints showed evidence of free fluid. Large doses of sulfanilamide resulted in no improvement except that the facial lesion did not spread. Agglutinations were again negative. The white count was 5000. Her condition improved in the course of two weeks and the facial lesion cleared up. At this time an intradermal test with brucella antigen was done. Twelve hours later, the original severe clinical picture reappeared including the erysipelas-like lesion over the face. A large local reaction developed at the skin test site with redness, swelling, lymphangitis and axillary adenitis. The local area sloughed, requiring three to four weeks to heal. The recrudescence of her illness subsided in three or four days, but convalescence was slow. She complained of soreness over the scalp and an area of thickening and tenderness was noted along the course of the right temporal artery.

Brucella vaccine alone intramuscularly was ineffective. However, a course of sulfanilamide and vaccine together caused striking improvement. The butterfly erysipeloid reaction on the face, recurring twice in association with the systemic reaction to vaccine, showed that it was a specific reaction.

Rheumatism again reappeared, after four months of good health. Agglutinations were negative. Sedimentation rate was 12 mm. per hour. Vaccine and sulfanilamide again resulted in striking relief of symptoms. Anginal attacks were controlled with nitroglycerine. Her blood pressure averaged 150 systolic and 90 diastolic.

Comment. A diagnosis was made of *chronic brucellosis* with recurrent acute attacks, mild hypertension and coronary heart disease with angina pectoris. The acute attack described was of particular interest because of the erysipeloid facial eruption reproduced by vaccine, and the temporal arteritis. No other cases of temporal arteritis were encountered in this series. Skin manifestations have been described in acute attacks by Simpson [23] and others. The long duration of symptoms is noteworthy. The agglutination test remained negative even after vaccine therapy.

Case 10. This male, aged 25 years, had his first contact with raw milk on a vacation at the age of 23 years. At that time, he developed "grippiness" with aching, weakness, fever, night sweats, diarrhea and upset stomach which lasted two or three weeks. Since then similar attacks had recurred. A stuffy cold and mild sore throat often appeared during the attack. He had observed a tendency to afternoon temperatures from 99° F. to 100° F., and diminished stamina. A hard day's work increased his fever and often precipitated headache, exhaustion and muscular aching. The attacks seemed to be caused by periods of overwork and gradually cleared up on adequate rest. He had never had any hemoptysis or chronic cough, and there was no history of exposure to tuberculosis.

Physical Examination. Temperature 99° F., pulse 85, blood pressure 110 systolic and 60 diastolic. He was well developed and nourished, and did not appear ill. Gen-

eral examination revealed nothing whatsoever. No foci of infection could be found. The tonsils had been removed. The lungs were clear. The heart was negative. The spleen was not palpable, and there was no general lymphadenopathy.

Laboratory Findings. Red blood cells 5,310,000, white blood cells 6000, hemoglobin 103 per cent; polymorphonuclears 54 per cent, lymphocytes 41 per cent, mononuclears 5 per cent. Urine was negative. Kahn and Kline tests, and agglutinations for brucella were reported negative by the state laboratory. Sedimentation rate was 3 mm. per hour. Roentgenograms of chest, sinuses and teeth were negative. Prostatic smear showed nothing. Skin test with brucella antigen was 3 plus.

Course. He was placed on high vitamin régime with rest periods and avoidance of raw milk. In four months his condition improved.

Comment. This patient was considered to have low-grade brucella infection with mild recrudescences. The relation of the subacute attacks and chronic symptoms to physical and mental strain observed in this case was also noted in others.

Case 35. This female, aged 15 years, had spent her entire life on a farm and had always drunk large quantities of raw milk. The herd was heavily infected. For six or seven years she had had migratory aching, stiffness and soreness in her knees, ankles, elbows, shoulders, wrists, hands and back. She suffered from frequent colds but gave no history of "grippe." She had occasional night sweats, tired easily and was nervous at school.

Physical Examination. Temperature 100° F., pulse 81, blood pressure 110 systolic and 90 diastolic. She was well developed and nourished and did not appear ill. No objective evidence was found of joint disease, although she complained of subjective pain in the wrists, knees, left elbow and hands. The sinuses were clear. Her teeth were in good repair. The tonsils had been removed. The heart and lungs were negative. The spleen was not palpable, and there was no glandular adenopathy.

Laboratory Findings. Red blood cells 4,670,000, white blood cells 12,900, hemoglobin 84 per cent, polymorphonuclears 50 per cent, stabs 6 per cent, lymphocytes 38 per cent, mononuclears 6 per cent. Urine was negative. The state laboratory reported Kahn and Kline tests and agglutinations for brucellosis negative. Roentgenograms of her chest, sinuses, and knees were within normal limits. Electrocardiogram was negative. Sedimentation rates on repeated examinations ranged from 8 to 12 mm. per hour. Skin test for brucellosis was strongly positive accompanied by a local slough. Her temperature, checked repeatedly, always ranged between 99° and 100.3° F. in the afternoons.

Comment. Chronic brucellosis of the type described in this case was encountered usually in the younger age groups. Little fluctuation was observed in the severity of the symptoms. The rather marked joint symptoms and myalgias with no objective findings in the joints were a striking feature. The normal sedimentation rate and absence of heart disease or electrocardiographic changes were useful in differentiating this form from rheumatic fever.

Case 38. This female, aged 44 years, had used raw milk until approximately 32 years of age. Since then exposure had been irregular, chiefly limited to several vacations in the country each year.

She had been a tuberculosis suspect for 25 years because of persistent afternoon temperature, exhaustion and night sweats. Hospitalization several times in sanatoria

had revealed no evidence of tuberculosis and a diagnosis had never been established. She had been subject to frequent colds and "grippe" for many years. This "grippe" was characterized by chilliness and less often by chills, fever, severe prostration, malaise and drenching sweats, and increase in her afternoon temperature. Colds and cough sometimes appeared at the beginning but more often during the course of the "grippe." For two years dyspnea on exertion and afternoon swelling of ankles had been noted. In January 1939, she had an abrupt onset of a tight aching substernal distress radiating into the neck, accompanied by a choking sensation which lasted three or four hours. Since then, similar attacks of short duration had occurred on exertion and were relieved by rest. Symptoms typical of peptic ulcer had recurred irregularly and once she had vomited blood. These symptoms were relieved by powders and Sippy régimes. For five years her periods had been excessive. There was no history of rheumatism or headache. The white count and blood pressure had always been reported "below normal."

Physical Examination. Temperature 99° F., pulse 78, blood pressure 120 systolic and 70 diastolic. She was well developed and nourished and appeared in good health except for rather pale mucous membranes. The head, eyes, ears, nose and mouth disclosed nothing abnormal. The vessels of the ocular fundi were normal. The lungs were clear. No cardiac enlargement was found. The sounds were of fairly good quality and no murmurs were heard. The liver and spleen were not enlarged. Several small fibroids were found on pelvic examination. Minimal pretibial edema was present.

Laboratory Findings. Red blood cells 4,160,000, white blood cells 4050, hemoglobin 70 per cent, polymorphonuclears 53 per cent, lymphocytes 37 per cent, mononuclears 9 per cent, eosinophiles 1 per cent. Urine was negative. Sedimentation rate was 6 mm. in one hour. The state laboratory reported Kahn and Kline tests and agglutinations for brucellosis negative. Roentgenograms of her chest showed nothing abnormal. No evidence was found of old or recent tuberculosis. The cardiac silhouette was within normal limits. A gastrointestinal series revealed some deformity of the cap but no evidence of active ulcer. Cholecystograms were negative. The electrocardiogram showed a QRS time of 0.12 second with a prominent S-wave in Lead I interpreted as intraventricular block. Skin test with brucella antigen was 4 plus. A lymphangitis, axillary adenitis and systemic reaction developed. She had severe drenching sweats, fever and a noticeable increase in her anginal symptoms for several weeks after the skin test.

Comment. This patient was considered to have chronic brucellosis, coronary artery disease with angina pectoris, and uterine fibroids with secondary anemia. No joint manifestations ever appeared in spite of the long history of infection and subacute recrudescence.

Case 23. This male, aged 45 years, kept his own goats and cows. Three years previously his son had had an acute febrile illness which was diagnosed as brucellosis by positive agglutination tests.

At the age of 41 the patient had had an illness which began with migratory joint and muscle pains but, in the course of a month, developed into a clinical picture of severe generalized aching and soreness, mental depression, nervousness, physical exhaustion, sweating, headache, vertigo, anorexia, indigestion and weight loss. After three months he had recovered sufficiently to return to part time work.

Since that time he had never regained his health but had continued to have varying degrees of migratory joint and muscle pains, headaches, recurrent dizziness, lightheadedness, indigestion, and exhaustion, worse in the wintertime. His joints had never been red or swollen, and his past health had always been excellent.

Physical Examination. Temperature 98.3° F., pulse 85, blood pressure 130 systolic and 70 diastolic. He was a thin but well preserved man. Tenderness was noted over the sterno-manubrial junction and the right trapezius. Otherwise, the joints and muscles were entirely normal. His eyes, ears, nose and mouth disclosed nothing abnormal. The tonsils had been removed. The thyroid was small. Nothing was found in the heart or lungs. The liver and spleen were not enlarged. The prostate was normal. Reflexes were all active and equal.

Laboratory Findings. Red blood cells 4,450,000, white blood cells 8350, hemoglobin 60 per cent; polymorphonuclears 60 per cent, lymphocytes 34 per cent, mononuclears 6 per cent. Urine was negative. Serologic tests for syphilis and agglutinations for brucellosis were reported negative by the state laboratory. Intradermal test for trichinae, negative. Brucellosis skin test, 2 plus. Sedimentation rate, 7 mm. in one hour. Roentgenograms of chest, teeth, hand, wrist and sinuses, negative. Uric acid, 3.2 mg. per cent. Basal metabolic rate, 2 plus.

Course. He was observed over a period of eight months. On a rest and high vitamin régime with removal of sources of exposure and two courses of brucella vaccine, he obtained approximately 60 per cent improvement.

Comment. This patient represents a type of case in which accurate diagnosis is difficult. However, in view of his son's acute attack during the patient's own illness, a clinical diagnosis of chronic brucellosis seems warranted. His temperature was consistently normal.

Summary

Brucellosis should be recognized as a chronic systemic infection capable of persisting through many years of a patient's life. Constant reinfection may have been a factor in this series since exposure had continued unchecked in most cases.

The clinical manifestations are variable. Nevertheless, various combinations of protracted fever, chronic fatigue and nervousness, recurrent "grippe"-like attacks characteristically with prolonged convalescence, headache, palpitation, gastrointestinal complaints, joint pains and myalgias should suggest chronic brucellosis. Cases representative of the clinical combinations most frequently encountered by the author have been presented.

It is suggested that coronary artery disease may be caused by chronic brucella infection. The temporal arteritis which occurred in case 6 indicates that the underlying pathology may be an arteritis of the coronary arteries. These observations require confirmation by the study of additional patients in areas where brucellosis is endemic.

Joint manifestations consisted of arthralgias, pain and stiffness in the involved joints and frequently moderate swelling. No redness was observed. A characteristic feature was the absence of residual deformity or permanent impairment of function. No relationship was found between brucellosis and rheumatoid arthritis. A normal sedimentation rate is of value in differentiating active phases of rheumatoid arthritis from brucellosis.

In this series the intradermal test was a reliable index of brucella infection. Only one case with a negative skin test presented a clinical picture

compatible with brucellosis. It is to be emphasized that neither the skin test nor the severity of the local or general reaction gives any reliable information as to whether the infection is active or latent.

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FAMILIAL SYRINGOMYELIA AND STATUS DYSRAPHICUS *

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During the last three years, we of the peripheral vascular department of the University Hospital have had the privilege of studying several members of a very interesting family. Various individuals of this group present signs and symptoms of impaired circulation to the extremities, disturbance of sensation in the lower limbs and feet, and a few members, similar disturbances in the hands. Slow-healing ulcers were present in the feet of some. Structural anomalies and the so-called stigmata of degeneration were present to an astonishing degree in nearly all the subjects examined. A striking familial resemblance was apparent in nearly all particulars, and deviation from normal seemed to follow a fairly harmonious pattern.

Case Reports

Fred Y. (I). Ran away from his home in Ireland at the age of 16 years. He fought during the Civil War, during which time he was bitten on the foot by a rattlesnake. Since that incident to the day of his death at 82 years, this individual was said to have had a great deal of trouble with his feet. Fred II states that he can remember his mother, during his childhood, bathing and dressing his father's feet.

After the Civil War, Fred Y I lived for a time in Missouri, then moved to Texas where he married and reared a family.

Fred Y. (II): April 24, 1936 to June 8, 1936. This 56-year-old man first noticed trouble with his feet 12 years prior to the above date, at the age of 44 years. He believed, however, that his feet had always been numb.

One evening on removing his shoes he noticed a blister on the tip of the fourth toe of the left foot. No special attempt was made to keep this area clean, and infection occurred. The toe became dark in color, and a foul discharge exuded from an ulcer which formed at the site of the blister. Complete healing occurred in about two months.

He was free of difficulty until two years later, at which time a blister followed by an ulcer appeared on the tip of the fourth right toe; the toe turned black, and the nail became loose and was removed. It was six months before healing occurred.

About one year later he experienced a burn on the right great toe while warming his feet on the kitchen stove and, although there was no pain or burning sensation, this burned area became a deep infected ulcer which required six months to heal. Small particles of bone sloughed out through the ulcer. There was never any marked degree of pain. On admission to the University of Oklahoma Hospital on April 24, 1936, a deep penetrating infected ulcer was present on the right great toe.

With the exception of the above complaints, the patient had been quite well and did not recall any illness with the possible exception of measles and probably malaria as a child.

* Received for publication June 21, 1939.
Research problem No. 1, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Systemic History: Essentially negative except for loss of weight in the past two years, 160 to 145 pounds.

Physical Examination: Well developed, well nourished male, 56 years of age, who did not appear ill. He had several carious teeth and marked pyorrhea.

Blood Pressure: 140 mm. Hg systolic and 90 mm. diastolic.

Abdomen: Negative.

Extremities: Hair distribution normal. Dorsalis pedis and posterior tibial arteries pulsating normally. Good arches were present in both feet. There was considerable disproportion in length of fourth and fifth toes in comparison with the others.

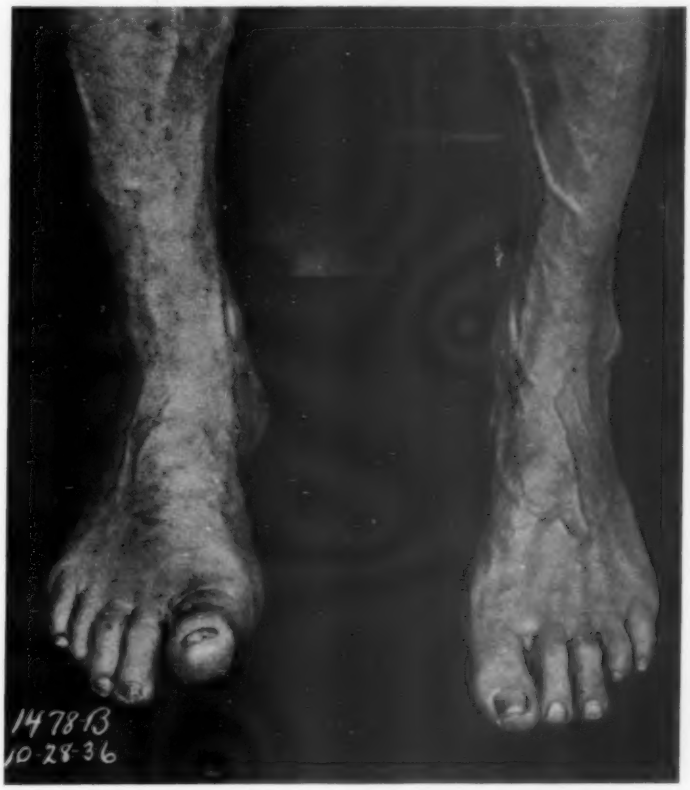

FIG. 1. *Fred Y. II* (October 28, 1936). Photograph shows marked deformity of the right great toe. Relative shortness of the fourth and fifth toes of both feet. Trophic changes.

The right great toe was considerably swollen and had a dusky color throughout. On the medial plantar surface there was a moderately deep clean ulcer, 2.5 cm. in diameter, with a slight discharge which had a very foul odor. On the lateral plantar surface there was a deep penetrating ulcer which had a diameter of about 5 cm., also with a very foul discharge. On the lateral plantar surface of the foot about 2 cm. from the base of the fourth toe there was a dry calloused ulcer about 1 cm. long and 0.5 cm. wide.

There was complete anesthesia to pressure, pain and thermal sensations over both feet on both plantar and dorsal surfaces. Pressure sense was unsatisfactory and delayed to a level as high as the knees bilaterally, and pain and thermal sensations were entirely lost as high as the knees.

Knee jerks and Achilles reflexes were present but sluggish even with reënforcement.

The hands were normal in appearance and exhibited no neurological findings.

Intradermal injections of histamine showed no reaction below the knees in either leg, although reactions were quite normal on thighs and forearms.

Roentgen-Ray 1: (May 9, 1936). The terminal phalanx of the right great toe showed a moderate osteoporosis. Lateral margin showed a loss of cortex and was somewhat irregular. The joint space was narrowed. Distal half of the first phalanx of the great toe showed also moderate atrophy and thinning of the cortex. A small bone fragment lay within the soft tissue medial to the terminal phalanx. The terminal phalanx of the fourth toe was small and irregular. There was similar irregularity of the head of the middle phalanx of the same toe. A small irregular deformity of the terminal phalanx of the fourth left toe was present. Roentgen-ray was suggestive of vascular or neurotrophic changes.

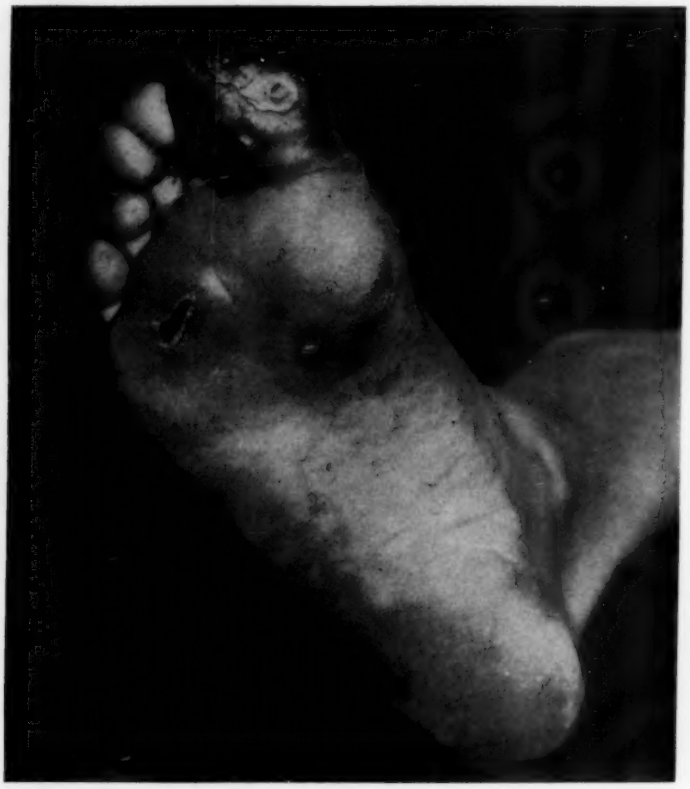

FIG. 2. *Fred Y. II* (May 11, 1936). Shows marked swelling of the great toe with several ulcers and two deep sinuses with foul discharge. Entire toe bluish in color. Dry calloused ulcer in mid forefoot.

The patient was admitted to the hospital where he was given complete bed rest and vasculator treatments for 50 hours at 70 mm. Hg suction and 20 mm. Hg pressure. Healing was practically complete on date of discharge, on the forty-fourth hospital day. The patient was advised to return for observation in one month.

The patient did not return for observation and was not seen again until July 6, 1937, at his home. At that time the great toe was entirely healed to all appearances. On the medial plantar surface of the right foot, however, there was a large ulcer about 4 cm. in diameter with a very foul discharge, necessitating a change of dressing four or five times a day. He was advised to return to the hospital but refused to do so.

Patient returned to the hospital July 20, 1938, for further observation. At that time no ulcerations were present, but the first and second toes on the right foot were markedly deformed. The distal phalanx was absent in each toe.

Roentgen-Ray 2: (July 20, 1938). The terminal and three-fourths of the proximal phalanx of the great toe were absent. The base of the proximal phalanx showed a somewhat increased density and a somewhat irregular distal contour. There was

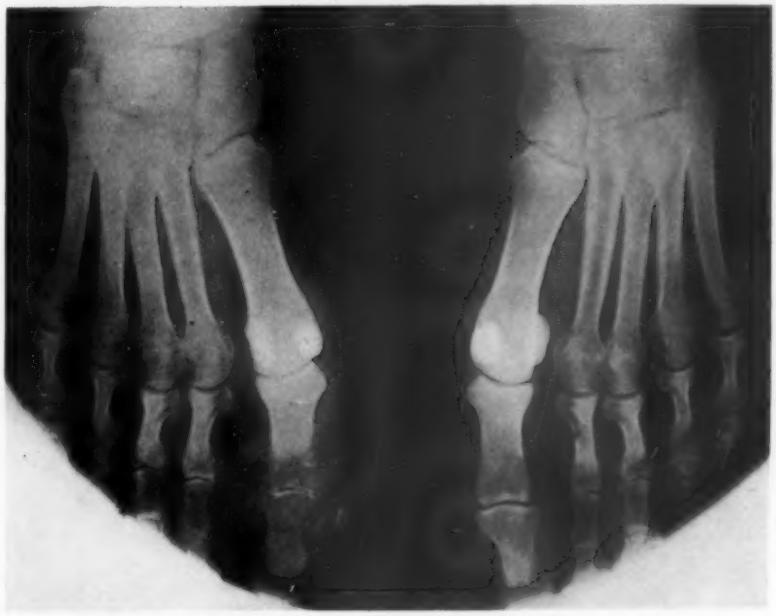

FIG. 3. *Fred Y.* (May 9, 1938). Osteoporosis of the right great toe. Deformity of the phalanges of the fourth toe of both feet. Narrowing of the articular spaces of both great toes.

narrowing of the tarsal-metatarsal joint of the great toe. The distal half of the proximal phalanx and the entire terminal phalanx of the third toe were absent, and there was almost complete absence of the terminal phalanx of the fourth. The inter-phalangeal joint was irregular. Roentgen-ray findings were consistent with neurotrophic changes in the phalanges.

Daisy Y. This 20-year-old girl was seen January 7, 1936, at which time she complained of sores on the feet, accompanied by marked coldness and numbness in both lower extremities.

She had noted that her feet were constantly cold, and only in extremely warm weather had they ever been warm and comfortable. They had always had a rather numb feeling, and were never very susceptible to painful sensations.

Lesions first appeared on the feet at the age of 16, when a clear blister became evident on the medial plantar surface of the right foot. There was no history of in-

jury, but infection and lymphangitis appeared, followed by local necrosis and a foul discharge. Four months were required to heal this lesion.

The feet became progressively more numb during the next three years. No more

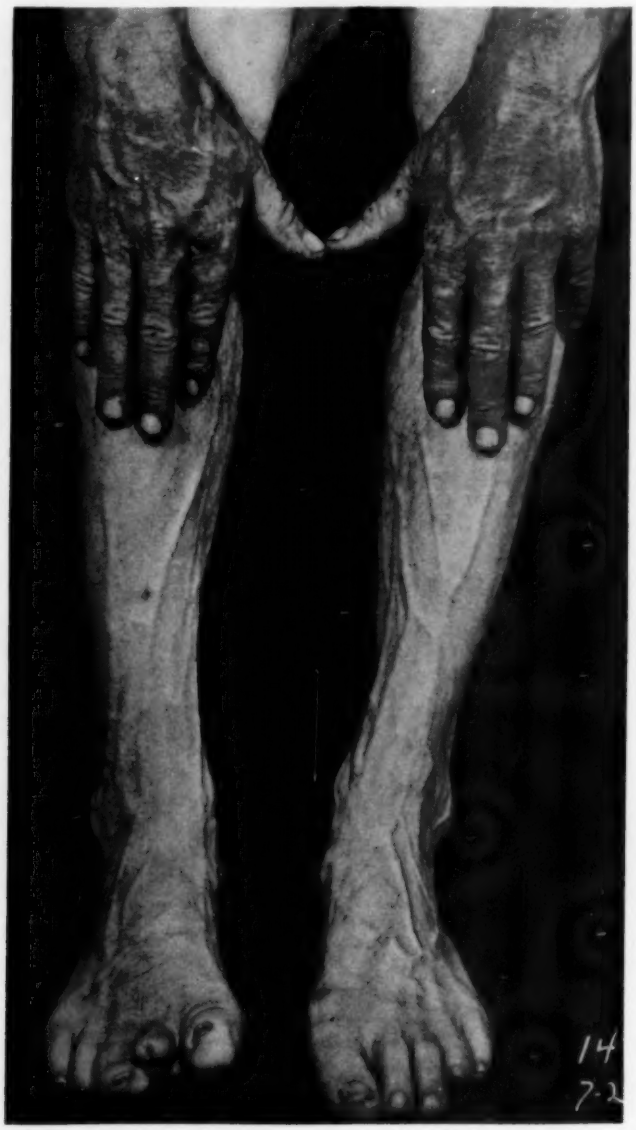

FIG. 4 (July 20, 1938). Photograph shows marked deformity of first and second toes of the right foot. There were no ulcers present at this time. Marked nail changes are shown.

skin lesions appeared, however, until January 1935, at which time blisters occurred on the medial plantar surface of the right great toe. The area around them became discolored but not painful, and an ulcer appeared which gradually grew larger and deeper, resisting all attempts at healing. Five months later a similar area became

involved on the left great toe which went through the same course and was equally stubborn in healing. Both lesions persisted up to this time of admission.

Systemic History: Negative.

Menses: Onset at 19 years of age, regular every 24 days, moderate flow. No intermenstrual bleeding or discharge.

Physical Examination: Well developed, well nourished young woman of 20 years, weight 100 pounds, height not recorded.

Extremities: Grossly negative except for large ulcers on the medial plantar surface of both great toes. These were rather deep and had a thin foul discharge. (Figure 7.) A bluish discoloration surrounded these areas.

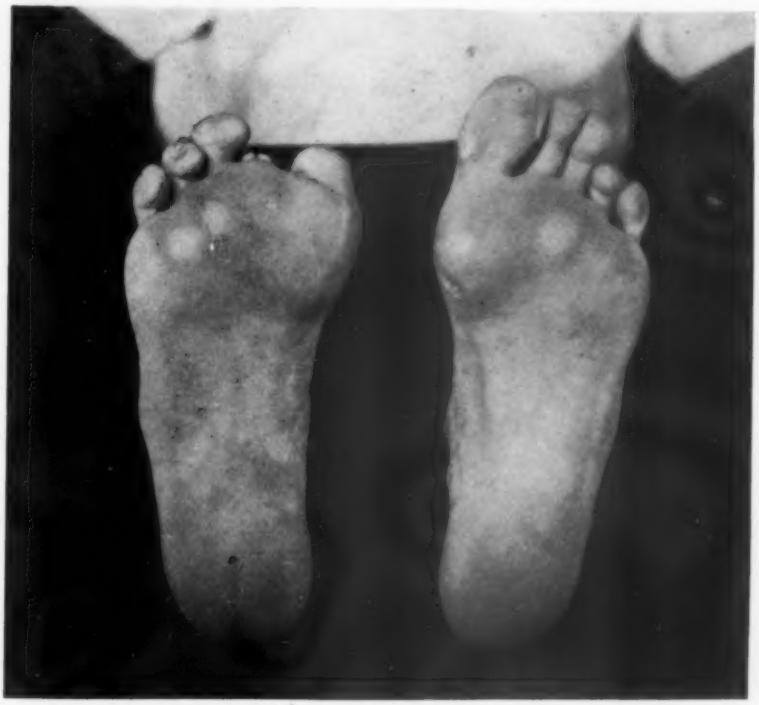

FIG. 5. *Fred Y.* Deformity of several of the toes on the right foot and shortening of the fourth and fifth toes on the left. This latter is apparently congenital.

The feet were cold and moist; the dorsalis pedis and posterior tibial arteries were pulsating, bilaterally. No marked change in color on elevation or dependency.

Knee jerks and Achilles reflexes were absent bilaterally even with reënforcement. Pressure sense, vibratory sense and position sense were present; but pain and temperature sense were absent bilaterally from distal portion of the lower legs.

Roentgen-Ray: (January 7, 1936). No pathologic findings as to blood vessels or bone.

Blood Count: Hemoglobin, 80 per cent; red blood cells, 4,400,000; white blood cells, 8,000; neutrophiles, 64 per cent; small lymphocytes, 36 per cent; spinal fluid, Wassermann and Kline tests negative; lymphocytes 2; globulin negative.

Course in Hospital: Absolute bed rest with heat cradle over both legs was ordered. Forty-eight hours of vasculator treatment, 60 mm. Hg suction and 20 mm.

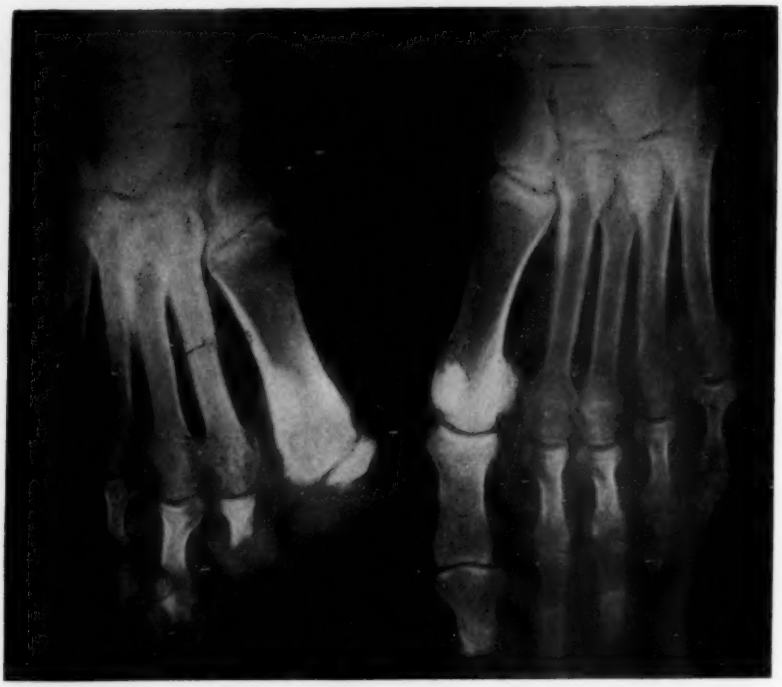

FIG. 6. *Fred Y* (July 29, 1938). Absence of several phalanges of the first to fourth toes on the right foot with irregularity of articular surface of the great and fourth toes.

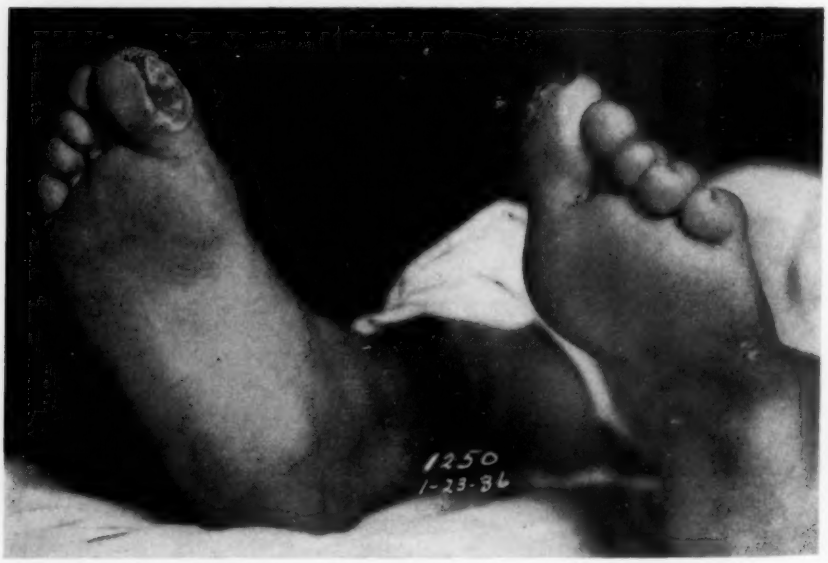

FIG. 7. *Daisy Y* (January 23, 1936). Ulcers on the medial surface of the great toes. Foul discharge. Immediately surrounding these lesions, the skin has a bluish discoloration. Healed ulcer present on lateral plantar surface of the left foot.

Hg pressure were given during her stay in the hospital. Right foot heated (96° to 100° F.) during treatments.

On discharge February 27, 1936, complete healing had occurred.

This patient was not seen or heard of again until she was admitted to the Los Angeles County Hospital on April 21, 1938, complaining of cold clammy hands and feet and ulcers on both feet of one year's duration. The systemic history was negative.

The hospital report disclosed the following description of the extremities. There was a deep necrotic painless ulcer at the base of the left great toe. The entire plantar

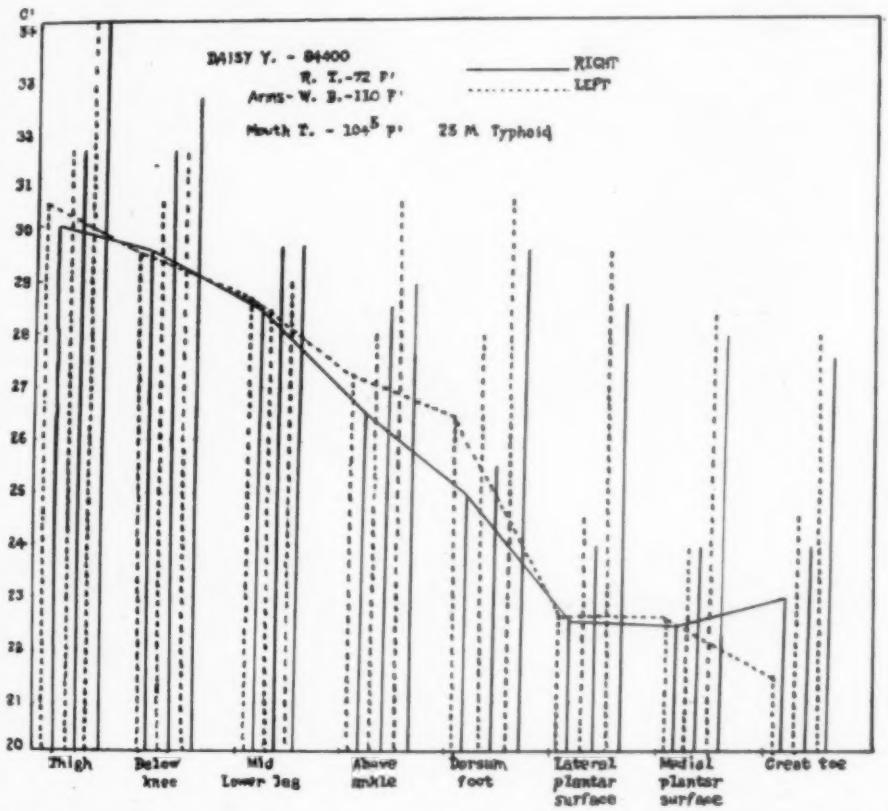

FIG. 8. *Daisy Y* (January 23, 1938). Marked difference in temperature readings between thigh and feet. Moderate rise in temperature is shown by reflex vasodilation (Landis) and greater rise after intravenous injection of typhoid vaccine. This reaction suggests marked vasospasm.

surface was reddened and slightly edematous. There was some red streaking on the medial surface of the leg; and slight left inguinal adenopathy with local tenderness. Dorsalis pedis and posterior tibial arteries pulsated normally.

The note of a neurological consultation mentioned cool perspiring hands and feet, hypesthesia of all the fingers and lower extremities from the knees distally; and impairment of touch sensation bilaterally to above the ankles. Position and pressure sensations were unimpaired. No motor weakness. No pathological reflexes. The consultant noted that he could not palpate the dorsalis pedis or posterior tibial arteries on either foot. There was scleroderma about the toes.

She was discharged from this hospital on June 3, 1938, before completion of the diagnostic study and treatment because she was not a legal resident of California. She was advised to return to the University of Oklahoma Hospital for further observation and treatment.

Rachel Y. June 21, 1938 to July 20, 1938. The patient was first seen in the outpatient department on February 27, 1935, at the age of 16, at which time she was

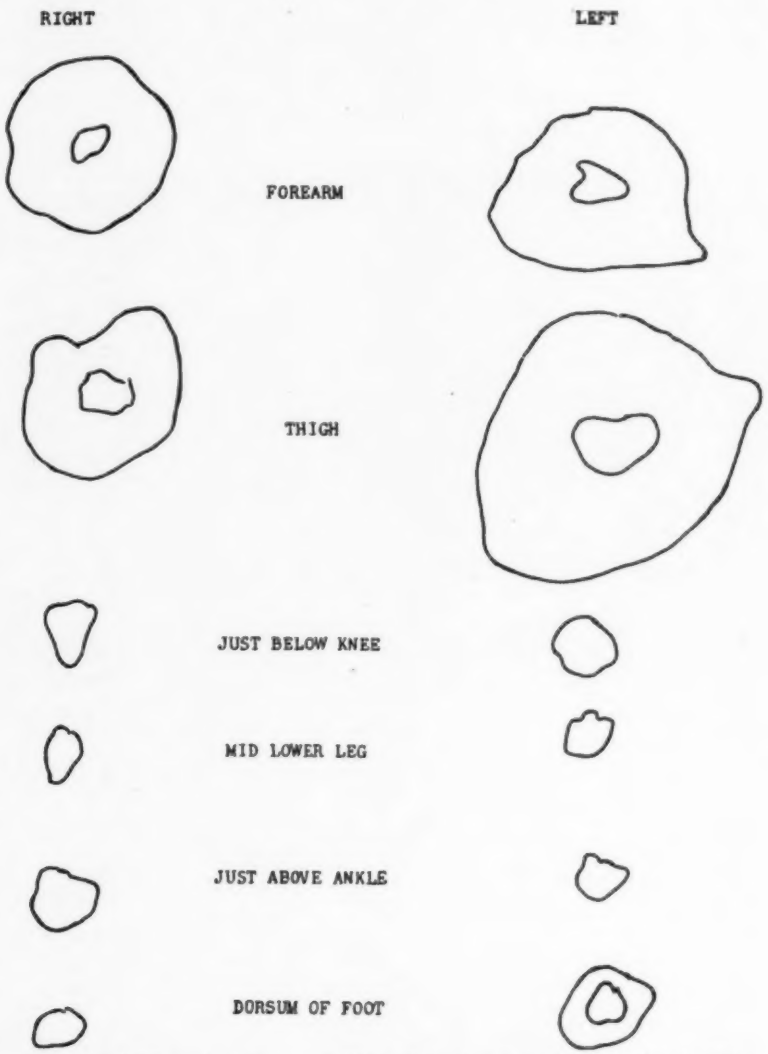

FIG. 9. *Daisy Y.* Histamine flares. 1–1000 histamine chloride solution intradermally.

complaining of amenorrhea and a purulent vaginal discharge. A diagnosis of nonspecific vulvo-vaginitis was made, which responded well to treatment.

She was seen again June 21, 1938, when the following story was obtained:

Ever since childhood the patient had been conscious of marked sweating of the feet to such a degree that she could at almost any time "wring water from her stock-

ings." Because of this condition she preferred going barefoot when at all possible. During these times she cut her toes many times, causing bleeding but never pain. Until the last few years she was able to appreciate pain elsewhere on the feet and extremities, but she believed there had been a gradual spread of numbness and anesthesia, finally involving both feet in their entirety.

Paresthesias were frequent; she at times had a feeling that stickers were present on the soles of her feet, a sensation so real that she occasionally removed her shoes and stockings in order to examine her feet.

Feet were cold to touch at all seasons. When exposed to moderate cold, feet and hands turned white, then blue and finally, on warming, became quite red. Aching was present in the arms when these were cold. Nails had had a tendency to turn black occasionally, at which time they broke quite easily. She had considerable difficulty in

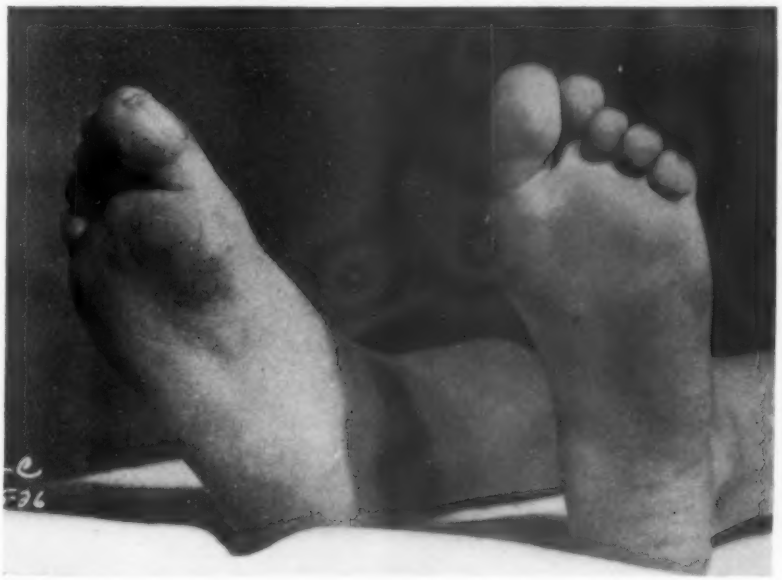

FIG. 10. *Daisy Y* (February 25, 1936). Approximately one month after admission. Heat cradle, vasculator treatments and absolute bed rest. Ulcers are almost completely healed.

walking at night, and stumbled and bruised her toes and shins when she made the attempt.

About one year prior to admission a clear blister appeared without known provocation, on the medial plantar surface of the left great toe. Most of the toe became very pale except at the base, where the skin showed a dark blue discoloration. An ulcer with a foul discharge soon appeared at the site of the blister, lymphangitis followed, and finally marked left inguinal adenopathy. Alcohol dressings were applied, and the ulcer healed in about 10 weeks.

Systemic History: Negative except for late onset of menses at 17 years of age.

Physical Examination: Fairly well developed, well nourished girl of 18 years. She did not appear ill. Weight 105 pounds. Span 66 inches. Height 65 inches.

Extremities: Appeared normal except for a ragged unhealthy appearance of the toe nails. The feet and hands were cold and clammy. Large beads of perspiration were present on the feet.

Dorsalis pedis and posterior tibial pulsation were absent bilaterally on several examinations. There was complete anesthesia to all sensations in all the toes. Tactile sensation was present but reduced, pain and thermal sensation were absent over the distal half of the lower legs. Only extremes in heat and cold could be felt from this region up to the knees. Sensation elsewhere on the body was normal. Vibratory sensation was reduced below both knees. The sense of position of the big toe

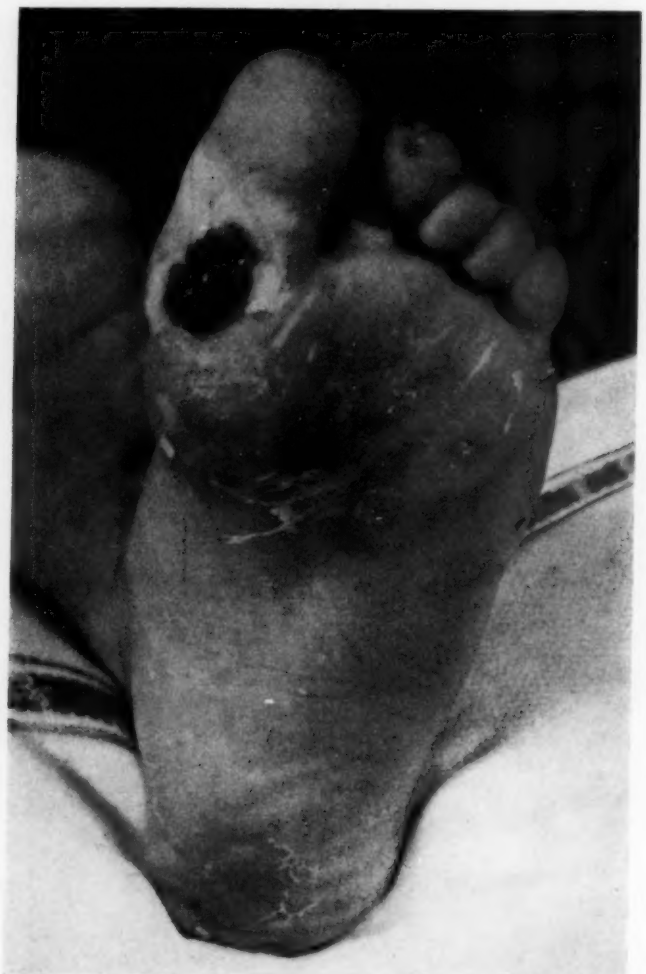

FIG. 11. *Daisy Y* (July 19, 1938). Ulcer present on junction of great toe and plantar surface of foot. Foul discharge. Deformity of second toe shown. (Photograph through courtesy of the Los Angeles General Hospital.)

was inaccurate. Heel to knee test showed marked ataxia bilaterally. She stumbled a great deal when walking with eyes closed. There was pastpointing on the finger-to-nose test. Romberg station was unsteady. Deep reflexes were present and active.

Arthur L. Y. Aged 48. This patient was examined at his home on July 10, 1938. He had been perfectly well until the spring of 1918, while serving with the A.E.F. A blister then appeared on the medial plantar surface of the right great toe, which was not

preceded by trauma. The patient was treated at the infirmary. He wore a cutout shoe, and healing occurred in about six weeks. He was free of any trouble thereafter until 1921, when a blister appeared in that same location, requiring about a week or so to heal. There was no recurrence until March, 1923, when a blister, followed by a deep ulcer, appeared on the tip of the fourth toe of the left foot, making hospitalization necessary for several weeks. On his discharge he was advised to use crutches until healing was complete. This required five months.

In November, 1923, a large "black blister" the size of a silver dollar appeared on

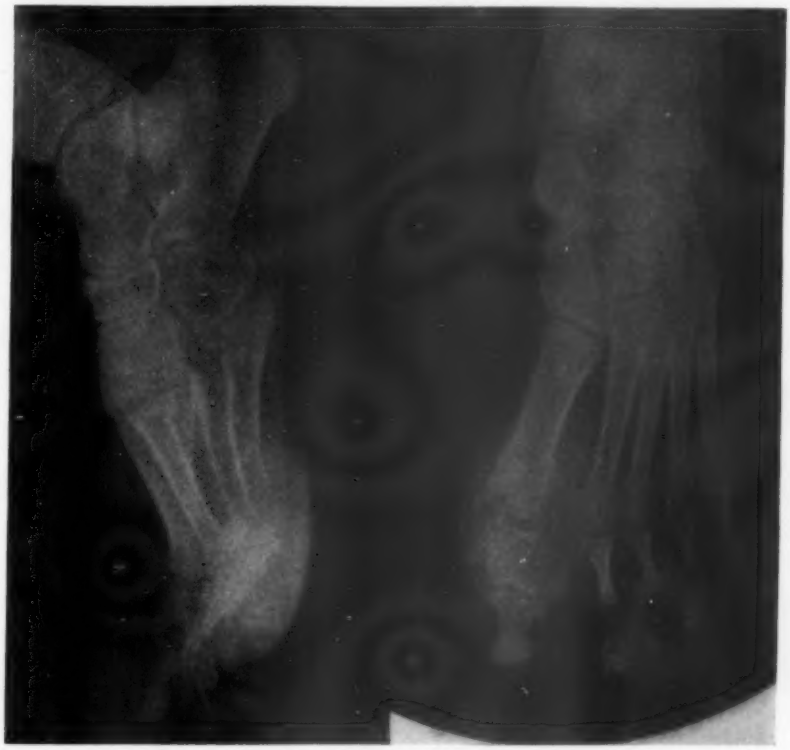

FIG. 12. *Daisy Y* (July 19, 1938). Reading: Considerable alteration of the structures of the phalanges of the great toe bilaterally. In the right foot there are punched out rarefied areas adjacent to the joint spaces between the phalanges. Joint surfaces are extremely irregular and are separated by an interval. The left great toe joint space is practically obliterated and the areas of rarefaction are less sharply defined. Considerable soft tissue swelling about both great toes. W. L. Stittson, M.D. (Through the courtesy of the Los Angeles General Hospital.)

the lateral plantar surface of the left foot. This became gangrenous in about four days. A surgeon excised the gangrenous area on the sixth day. Five months were required for healing.

Since then, except for nearly the entire year of 1936, when he was resting, the patient had never for more than 30 days at a time been free from blisters, followed by indolent ulcers requiring long periods of time to heal.

During the winter of 1926, the entire right foot was covered with blisters, superficial sloughs and discharging ulcers of various sizes, many of them confluent. About three months later similar lesions of the same extent appeared on the left foot.

The feet were exceedingly painful. Nine months were required for healing. During this time he was given a course of salvarsan and mercury, although repeated negative blood Wassermann tests had been obtained. No improvement resulted from this treatment.

In 1930 a roentgen-ray examination showed extensive osteomyelitis involving the bones of the right foot. Several minor operations were undertaken and small segments of bone removed. Several large ulcers discharging sero-purulent material were

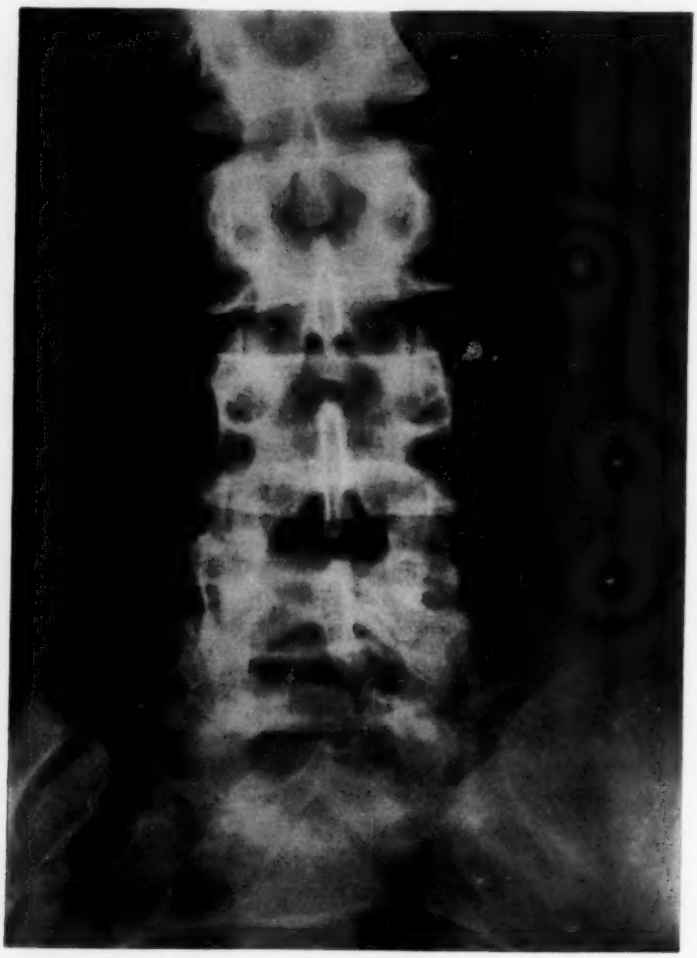

FIG. 13. *Rachel Y* (August, 1938). Spina bifida occulta.

present on this foot and continued to be present until 1935, when the entire lower leg became insensitive to pain or touch. A Gritti-Stokes amputation was done at a Veterans' Hospital during that year.

Owing to the enforced rest following amputation of the right leg the left foot became completely healed, was painless, and was free of any trouble for the entire year of 1936. In November 1936, however, while standing on a ladder, the patient had a feeling of "something breaking" in the left foot accompanied by moderate pain. On examination he found on the ball of his foot a large blister which rapidly changed

into a deep ulcer discharging foul material. Since then dressings have been required twice daily. If he rests in bed for several weeks the lesion almost entirely fills in with tissue but if weight is again placed on the foot the lesion breaks down and a deep discharging ulcer appears. At present he feels fairly well, but must apply four to five dressings to the foot daily.

No paresthesias or hyposensitivity in the extremities were noted until 1928, when the patient found that he had to watch where he placed his feet in walking. Shortly after this he began to notice that he was insensitive to all but extremes in tempera-

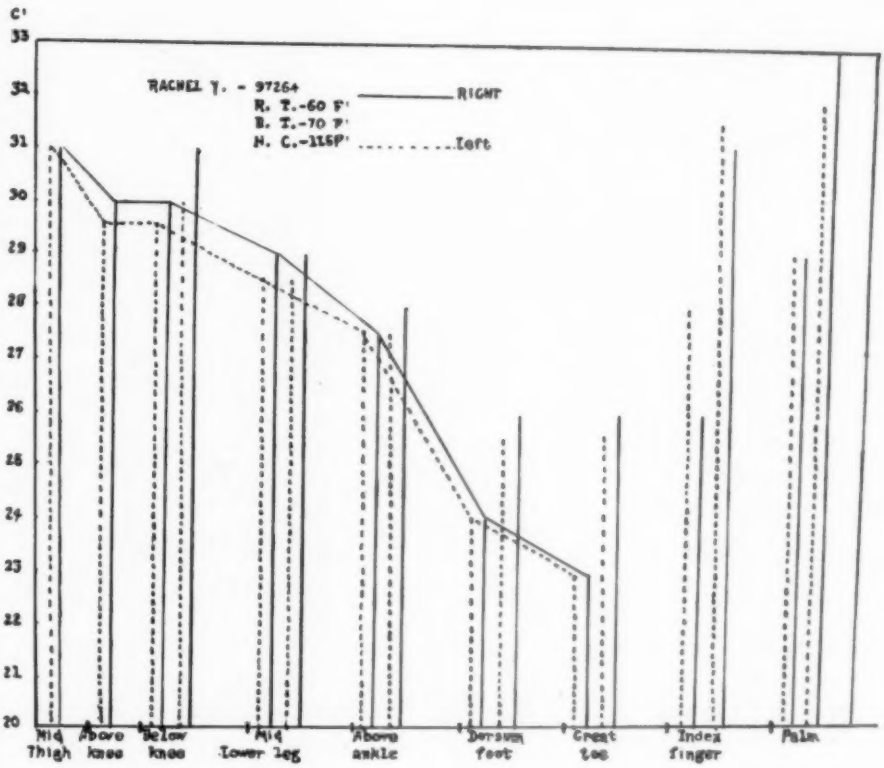

FIG. 14. *Rachel Y* (August, 1938). Shows marked difference in temperature between the thigh and foot bilaterally and relative coldness of the distal halves of the lower extremities. Vasodilatation and increase in temperature are shown after the body has been enclosed in heat cabinet, temperature 115° F. with extremities exposed at 76° F.

ture either hot or cold, and he had difficulty in interpreting which of these was present. This difficulty was noticeable only in the feet and lower legs.

Systemic History: Negative except for nocturia two to three times and day frequency three to four times with some little difficulty lately in starting the stream. Weight varied very little, averaging 130 to 135 pounds.

Past History: Measles, mumps, typhoid in childhood. Pneumonia at 15 years of age. Malaria in 1917. Appendectomy and herniotomy in 1934.

Physical Examination: Well developed but not well nourished man, 48 years of age. Did not appear ill. He was ambulatory, used crutches and had an artificial limb on the right. The left foot was swathed in bandage material.

Extremities: Right leg amputated at the knee joint; the stump was in good condition, the musculature of the thigh atrophic.

Left leg, complete anesthesia below the mid-lower leg. Achilles reflexes and knee jerks were hypoactive, plantar reflex absent.

The toes were deformed and atrophic, and there was a large ulcer, about 2″ by 2″ on the ball of the left foot, which had a foul seropurulent discharge. No hypesthesia

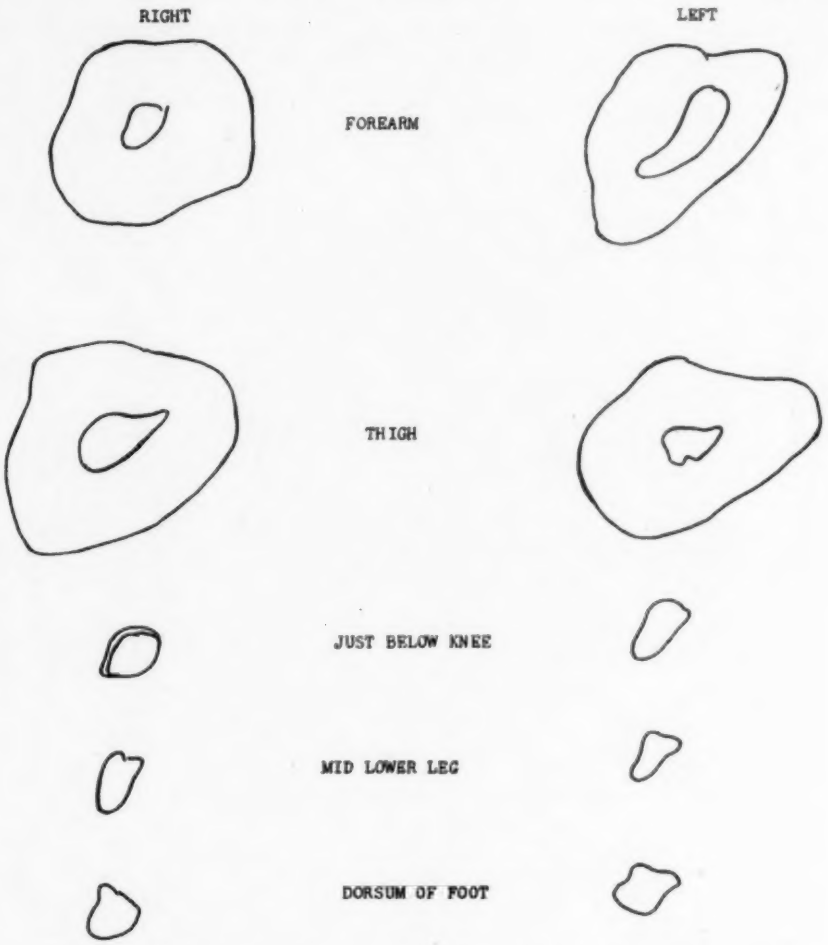

FIG. 15. *Rachel Y.* Histamine flares. 1–1000 histamine chloride solution intradermally.

was noted in the hands. The biceps and triceps reflexes were active (plus two), and the Hoffman reflexes were negative.

James A. Y. Aged 16. This boy was examined at his home on June 10, 1938. He had apparently been a normal and healthy child until the age of six years but had not been very well since that time. At this age he had a severe attack of measles complicated by pneumonia and heart trouble.

At the time of his examination he had considerable dyspnea on exertion and developed obstinate chest colds and bronchitis very easily. There had never been any noticeable cyanosis or edema. Systemic history was otherwise negative.

This boy noticed painful white hands and feet on exposure to extreme cold, which changed to a bluish red on warming. He stated he had never observed any difficulty in appreciating heat and cold nor had he observed insensitivity to pain. His feet tingled and went to sleep very easily, and a blow or bruise was followed by anesthesia of the affected area for several minutes.

Physical Examination: Poorly developed and poorly nourished boy, 16 years of age. Somewhat retarded, but coöperated well.

Head and Neck: Scalp was negative. Eyes: pupils reacted normally. Teeth were good. Tonsils were hypertrophied. High arched palate.

Chest: Respiratory excursions equal and symmetrical. No areas of impaired resonance.

The point of maximum impulse was 13 cm. from the midsternal line and was diffuse. Percussion showed the heart border extending to the axillary line.

FIG. 16. *Arthur Y* (June 10, 1938). Deformity and displacement of the fifth toe of the left foot owing to secondary infection and loss of bone.

A systolic and diastolic murmur could be heard at the base and at the seventh interspace on the right near the sternal border. The diastolic murmur could be heard along the left sternal border between the third and fifth intercostal spaces.

Blood Pressure: Right 140 mm. Hg systolic and 80 mm. diastolic. Left 135 mm. Hg systolic and 80 mm. diastolic.

Popliteal Blood Pressure: 150 mm. Hg systolic and 80 mm. diastolic, and equal bilaterally.

Abdomen: Negative.

Extremities: Negative except for marked painless flat feet. There was no clubbing. He was unable to appreciate any but extreme thermal changes. Pain sensibility was reduced on the soles of the feet, intact on the palms. The dorsalis pedis and posterior tibial arteries were pulsating normally.

Reflexes: Normal reflexes present and active, no abnormal reflexes elicited.

Virginia Y. Aged 17. The patient was examined at her home on June 10, 1938. She had always had good health except for a severe attack of scarlet fever at seven years of age. She had noted as long as she could remember that her feet would sweat a great deal and that two or three changes of stockings daily were necessary for comfort. She had also constantly suffered with cold feet. When exposed to cold both hands and feet would turn dead white and remain so until warmed artificially, whereupon they turned a reddish blue and became quite painful and throbbing.

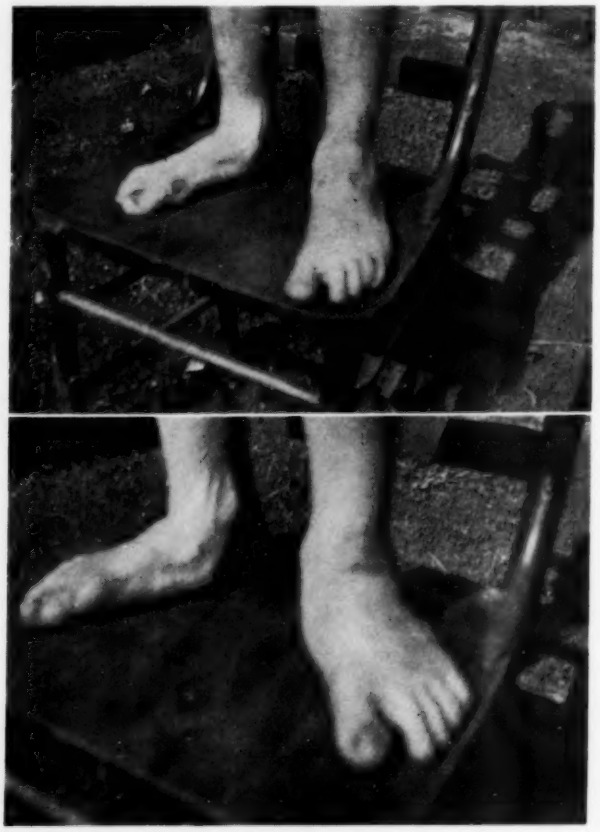

FIG. 17 (*Above*). *Murrel Y* (June 10, 1938). Painless flat feet, marked.
FIG. 18 (*Below*). *James Y* (June 10, 1938). Painless flat feet, marked.

For three or four years prior to examination she noticed that she was quite apt to burn her hands if she was not very careful. Once when testing an iron for heat she placed the palm flat against the ironing surface and felt very little warmth, but later in the day a large blister appeared, covering the entire surface, and the hand was stiff for many days.

She experienced marked difficulty in walking, especially in the dark, when she was very apt to stumble and bruise her feet; and even during daylight she had to be more or less aware of where she placed her feet. When walking a considerable distance the feet would burn a great deal, yet when she palpated them they were noticeably cold and wet.

Bruises and blows to the feet resulted in anesthesia to the affected area for hours afterward. She was frequently troubled with blisters on both feet, but none was present at this time. There had never been any ulcers on the feet.

Systemic History: Negative except for late onset of the menses at the age of 17.

Physical Examination: Well developed and nourished girl, 17 years of age, intelligent and coöperative. There was a slight diffuse enlargement of the thyroid.

The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic.

The extremities was superficially normal in appearance.

The biceps and triceps reflexes were hyperactive (plus two). The knee jerks and Achilles reflexes were obtained with reënforcement. The plantar reflexes were positive.

The position sense of the big toe was inaccurate bilaterally.

There was an irregular response to heat and cold stimulation on the dorsum of the

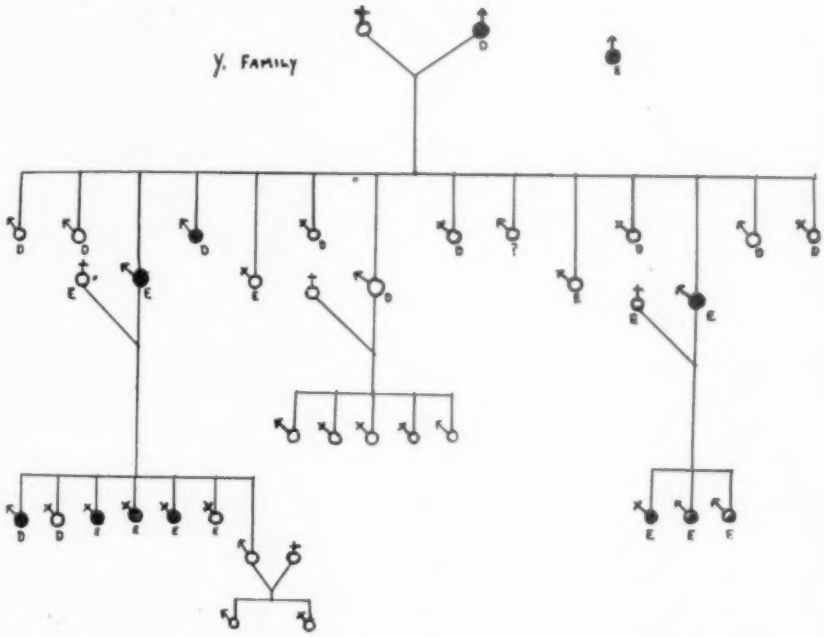

FIG. 19. Family tree. Blackened areas indicate individuals with the disease, confirmed either by examination or through family history. The letter (E) indicates those examined.

feet and lower legs and dorsum of the hands. Application was slow. Pain sense was likewise irregular. The soles of the feet and the palms of the hands were insensitive to thermal and painful stimuli, but were sensitive to pressure.

The hands and feet were cold and clammy.

F. Y. S., 33, married, housewife. This 33 year old woman was seen for the first time in the outpatient department of the University Hospital on February 5, 1936. The following history was obtained:

She had been well until four years before, at which time she noticed a painless blister on the ball of the right foot. This lesion subsequently ruptured, and the underlying tissue became infected and discharged very foul material. She consulted a physician who apparently removed some necrotic tissue. The lesion was very slow in healing, requiring six months, three of which were spent on crutches.

About three months later a blister appeared on the medial plantar surface of the big toe of the right foot. This became infected and was followed by lymphangitis and right inguinal adenopathy. Gangrene soon occurred, necessitating removal of the distal half of the toe. Eight to ten months were required for healing. During the latter months of this process the large toe on the left foot became similarly involved and blisters, followed by gangrene, became evident on the tips of the four smaller toes.

Since the onset the patient had never been free of trouble. There had been a succession of blisters, followed by lymphangitis and ulcer formation, which required months to heal. These were always on the plantar surface of the toes and distal half of the feet.

The patient had noted for the past four years that her feet had a dead feeling and that she was able to appreciate only extremes in heat and cold, and then only after exposure to these temperatures for some time. During this period she had burned her feet on several occasions, resulting in slow-healing painless ulcers. During the last few months there had been considerable pitting edema of both feet. There were no seasonal variations in degree of involvement. The fingers were numb at times.

Systemic History: Negative except that menstruation was late in onset, at 20 years of age.

General Physical Condition: Negative. Pulse, 80. Respirations, 20. Temperature, 98.4°.

Extremities: Grossly normal in appearance except for loss of the distal phalanx of the right great toe and distal phalanx of both small toes. There was a foul discharging ulcer at the site of the proximal phalangeal joint of the right great toe. To palpation there was a marked difference in temperature between the thigh above the knee and the foot. Bilaterally, the temperature decreased rapidly as palpation was carried from the knee to the foot.

There was hypesthesia of both lower extremities from mid-lower leg downward and of the palms and dorsa of the hands bilaterally. The feet were practically anesthetic to pain and thermal stimulus. Response to pressure stimulus was slow and not very clear. The position sense of the big toe was unstable but fair. There was slight ataxia in the heel to knee test bilaterally. Vibratory sensibility was reduced.

No pulsations could be felt in the dorsalis pedis arteries of either foot. The posterior tibial artery was faintly pulsating on the right, not felt on the left.

Treatment: Complete rest in bed was impossible though the patient was advised to obtain as much rest as possible. Thirty-four hours of vasculator treatment were given with suction 60 mm. Hg, pressure 20 mm. Hg. Considerable objective and subjective improvement was noted on discharge, March 19, 1936, although the ulcer was not healed. From the date of discharge on March 19, 1936, the patient was not seen again until June 13, 1938, at which time she was examined at her home in Long Beach, California. Physical and neurological findings were much the same as on discharge. There was a deep ulcer about 2 by 2 cm. on the medial surface of the right great toe, which had been present for several months. The patient stated that several fragments of bone had sloughed from this area. Roentgen-ray was not available.

Summary of Family History

The individual representing the first generation of this family, as far as this record is concerned, has been dead many years. He was not examined, but the evidence is strong, from the information given by the members of the second generation, that this man had a severe disease of the feet throughout the greater part of his 81 years of life.

Of 14 members of the second generation, only five are living; three of these have been examined by us and one by Dr. Lee Rice of San Antonio, Texas. Two of this generation, examined by us, and Cora, examined by Dr. Rice, are apparently free of the affliction. There is strong evidence, from the family, that David, another member of the second generation, died with gangrene of the feet. He had not been examined, however, nor have we been able to obtain any medical report concerning him.

Of questionable importance in this group is the history of two other members dying of diseases referable to the nervous system, namely, Charles, who died of paralysis, and Geminia, who died of meningitis. This may have been coincidental.

In the third generation, seven of a possible 15 individuals have been examined. Five of this generation, the children of Charles, are to date untraceable. John, a son of Frederick, is unavailable. Leona, a daughter of Frederick, died of appendicitis at the age of 12. There is no history of her having had the disease. David, another son of Frederick, died with a peculiar foot affliction with gangrene at the age of 13; but a medical history is lacking. Gracie Y., a daughter of Frederick, had a typical history and findings of anterior poliomyelitis, but examination was fruitless in her case for purposes of this report.

Of the six remaining members of this generation all have shown some degree of dissociation of sensibility in the feet. Some have exhibited changes as high up as the knees. Two have had impairment of sensation in the hands. Although the loss or decrease of pain and temperature sensibility is the most important neurological finding in these patients, four of those examined showed some disturbances in the sense of position.

Purposely left out of the individual reports were some findings common to all patients examined in both generations except the two women in the second generation. All appeared to have been poured from a common mold. All were tall and thin, and the span averaged ¾ inch more than the height in all in whom this particular finding was checked. The hands and feet were narrow and long, the fingers, except in Murrel, son of Arthur, were long and slender. All had high arched palates. Two had a moderate pes cavas and two had marked painless flat feet. The scapula in all had a definite tendency toward winging. Murrel, aged 14, had no dissociation of sensibility, although marked deformity of both little fingers was present.

Four of the third generation, three girls and one boy, gave histories quite suggestive of Raynaud's phenomena, although attempts to precipitate these symptoms in one girl, Rachel, were not successful in our laboratory.

Nearly all of the individuals examined showed evidence of circulatory inadequacy in the feet and lower legs. Histamine flares were markedly reduced below the knees in the three to whom this test was given. The vasomotor gradient was steep both clinically and on laboratory examinations in all those in whom infection was not of sufficient magnitude to change the local temperature.

Six of the individuals examined have had painless slow-healing ulcers of the feet. Three gave a history of bone sloughing from these ulcers. Two gave a history of self-amputation of some of the toes. One had had an amputation at the knee-joint because of deformities and osteomyelitis.

Roentgen-Ray: Trophic changes were present in the bones of the feet in two patients, and there was evidence of loss of bone structure in the phalanges. In one patient, a roentgen-ray of the lumbar spine was taken disclosing a spina bifida occulta.

In three patients there was a late onset of menses at 17, 19, and 20 years.

Comment

Before presenting these cases we made a careful search of the literature, in order to unearth, if possible, reports of a familial condition which though resembling syringomyelia, is yet of a more static nature. It seems to represent a constitutional abnormality of which syringomyelia remains, so to say, one potentiality, but which may find partial expression in the most varied local anomalies and clinical manifestations, which have not the progressive character of that syndrome.

Syringomyelia has long been recognized as a chronic progressive process in the spinal cord, the result of glial proliferation which leads in time to necrosis and cavity formations in that organ. The results of this progressive gliosis are then expressed in typical progressive atrophies and sensory disturbances affecting various parts of the trunk and extremities, according to the particular localization of the original cord lesion.

In syringomyelia proper, the most characteristic location of the lesion is the central portion of the cord. A lesion so placed will interfere with the decussating fibers carrying pain and temperature sensation, and a decrease or complete loss of sensibility will occur in the region in which these fibers originate. The sensory loss will be on only one side if the lesion affects the posterior gray horn on that side, but on both sides if the commissure is involved. Extension into the anterior horns will cause weakness of the muscles in the segmental distribution. The pyramidal tracts are sometimes involved, in which case a spastic type of paralysis may ensue.

Reports in the literature of the English language are rather meager concerning the condition status dysraphicus, which is now generally accepted as the constitutional substratum underlying syringomyelia. With this in mind, we are reporting the above patients as representing either a strong familial tendency toward syringomyelia, or, what is more likely, as examples of status dysraphicus, a similar and probably closely allied condition, but one showing evidence of widespread vasomotor and trophic disturbances of more varied kinds than the former, and exhibiting little of the tendency to progress, which has long been recognized in syringomyelia.

Considerable debate has arisen with reference to the familial appearance of syringomyelia, some authors denying that this affection is congenital and

insisting that if it appears more than once in a family group this is a pure coincidence without heredo-biological significance.

Schlesinger,[1] who wrote an authoritative work on the subject of syringomyelia in 1902, in which he discussed 260 cases of this condition, referred to several reports of what were claimed to be familial cases of syringomyelia. These were the cases of Ferrannini,[2] Nalbandoff,[3] Preobrajenski,[4] Krafft-Ebing [5] and of Verhoogen and Vandervelde.[6] Schlesinger entirely rejected these reports, of which only the last-named reported autopsy findings, and insisted that there is no such thing as congenital syringomyelia; hence, any so-called familial cases were of no interest. In the case of Verhoogen and Vandervelde he said that it was probably not syringomyelia. Here the condition affected two adult sisters and one brother who were children of alcoholic parents, and thus inherited a congenitally inferior nervous system. The disease came into manifestation insidiously, at the ages of 8, 12 and 12 years, respectively, unobserved at first by the patients, but followed by a long history of trophic disturbances in muscles and nails, cyanosis of limbs, livid and cold hands and feet, and the classic thermo-anesthesia of syringomyelia in high degree.

In 1903, Bruns,[7] reviewing these earlier cases, reported one of his own in which four of five children of healthy parents had deep symmetrical gangrene of fingers and toes, with ulcers of the feet and dissociation of sensibility. He regarded this as a case of familial syringomyelia in the lumbar spinal cord. In each of these four individuals the symptoms had first been observed at about the age of 17. The condition was progressive, and in two of the cases amputation was later necessary.

Fuchs,[8] in 1903, was the first to give the name "myelodysplasia" to a syndrome which, he said, is a *picture of syringomyelia, but without progression.* In association with Mattauschek [9] he found the following characteristics present in myelodysplasia:

1. Weakness of the sphincters, enuresis persisting into adult life.
2. Syndactylism of the second and third toes.
3. Disturbances in sensation of the legs, of a dissociated type, in which thermo-anesthesia is most marked.
4. Cleft arches of one or more vertebrae.
5. Abnormal skin and tendon reflexes of the abdomen and lower extremities.
6. Deformities of the feet, clubfoot or flatfoot, often associated with trophic and vasomotor disturbances.
7. Skin changes, such as hypertrichosis, naevus and fovea coccygea.

To these, Bremer [15] later added the following:

1. Acrocyanosis of the extremities, especially of the fingers.
2. Crumpling of fingers, especially the little fingers.
3. Sternal anomalies, particularly infundibular thorax.

4. Inequality of the mammary glands.
5. Kyphoscoliosis.
6. Greater span than height.

While not all of these manifestations were present in every case of myelodysplasia, Fuchs [8] observed a striking tendency for several of them to be associated together in individual patients. He attributed the condition to a "congenital hypoplasia or dysplasia of the lower spinal cord." Mattauschek at the same time observed that in five-sixths of his cases, enuresis was the expression of an abnormality of the lumbar spinal cord, and not due to a psychic component as had been maintained. It was often accompanied by syndactylia, abnormal patches of hair, disturbed reflexes and hypesthesia for heat and pain. This myelodysplasia, this "syringomyelia without progression" was, as we shall soon see, synonymous with the status dysraphicus that was to be differentiated from syringomyelia by Bremer [15] nearly 20 years later.

In this same year (1909) Clarke and Groves [10] reported a familial case of sacrolumbar syringomyelia in a brother and sister aged respectively 23 and 15. Here the phalanges and metatarsal bones had undergone a process of atrophy and were found to have gradually disappeared.

Haenel,[11] on the basis of these various publications which showed the indisputable existence of syringomyelia with familial trophic disturbances, asserted that such degenerative stigmata as spina bifida, ear lobe anomalies, cervical rib, duplication of the central canal, meningocele, microgyria, and the like, prove that many patients have already brought along an anlage of syringomyelia, and also that there are rare cases of congenital gliosis. Further evidence of this congenital factor was produced when Lundgaard [12] observed (1913), a seven months' fetus, which was born with only one of its four limbs present, and with various other dystrophies. The child was autopsied nine weeks after birth, at which time the type of morphologic changes found in the spinal cord justified a diagnosis of beginning syringomyelia.

In 1919 Bielschowsky and Unger [13] published the modern conception which no longer recognizes any real difference between congenital anomalies of the gray substance and the central canal, on the one hand, and syringomyelia on the other. Their work was taken up by Henneberg,[14] in 1920, who demonstrated by autopsy of three spina bifida infants who died a few weeks after birth that the changes which bring about syringomyelic cavity formation begin very early, plainly in the intrauterine period, and that syringomyelia may be conceived as having its basis in a rudimentary form of spina bifida.

He suggested that the congenital anlage is probably very common, and is *inherited,* but that very special exciting factors are necessary to arouse active gliotic proliferation. It seemed clear that a faulty closure of the neural tube might give rise to the inclusion of embryonic cell rests in the spinal cord, which eventually result in gliosis and finally in cystic cavity for-

mation. He felt that this condition of "dysraphy" was responsible for many of the hereditary neurological diseases, and that it was the expression of an hereditary degeneration.

In 1926, Bremer [15] introduced the name *status dysraphicus* and published an epoch-making work on the subject. Here he placed on record his findings in 10 families in which he made an intensive study of heredodegenerative states, among which were the results of his studies in four cases that came to autopsy. As de Vries,[16] and later Riley,[17] pointed out, the clinical syndrome of Bremer's status dysraphicus is essentially that already described by Fuchs under the name *myelodysplasia*. Bremer made it clear that in order to understand this condition, which is widespread, it is necessary to examine the other members, the healthy individuals, in family groups in which some one member has a sufficiently severe disturbance to bring him to the doctor. Most of these dysraphic individuals are living a normal life and do not seek a physician's treatment. In a very recent article, Bremer [18] states that he continues to find, in the relatives who are not sick, "formes frustes" of the syringomyelic syndrome—a condition which does not show any progression, but in which vasomotor and trophic disturbances are very evident. He has repeatedly pointed out that this status dysraphicus is found not only in syringomyelic patients, but is systematically present in all diseases of the entire group of dysraphic disturbances. In the first of his 10 families, in which four generations and 25 individuals could be accounted for, the 15 who could be examined were all found to have the classic symptoms of syringomyelia. Most of them were not ill, however, and their stigmata would not have come to light if they had not been definitely looked for.

Curtius and Lorenz [19] have gone deeply into this subject, and conclude that dysraphicus is not only developmentally and anatomically, but also clinically, a thoroughly definite constitutional type. That the development disturbance is inherited was shown in 13 to 14 cases. They studied 32 cases of status dysraphicus and 17 of syringomyelia. Of the 32 cases of status dysraphicus 21 had striking nervous abnormalities, and 16 had marked mental disturbances. Examining at random 500 roentgenograms of the spinal column out of the archives of their department, they were amazed to find that 17 per cent of normal persons are dysraphic, a figure which Bremer accepts as correct. According to these authors, the relations of status dysraphicus go beyond the narrow field of syringomyelia. They state that dysraphic symptoms are being seen relatively often in other types of heredodegeneration. For example, status dysraphicus is found in many families with cases of Friedreich's ataxia and is frequently met with in patients with multiple sclerosis. But it appears, says Curtius, that we do not yet possess the requisite knowledge to systematize these conditions and that we are still unclear with regard to the relation of status dysraphicus to other organic nervous diseases. Investigation of the subject is rendered very difficult by the fact that the anatomic changes are accompanied by clinical symptoms in only a small fraction of the cases, so that they are usually an accidental finding

during examination of a patient who comes for some other apparently unrelated condition.

Passow [20] made the observation in 1934 that certain ocular conditions point to status dysraphicus. Systematic examination of over 70 patients presenting Horner's syndrome (ptosis, enophthalmos and miosis) showed, astonishingly, that in nearly all the 64 families represented, familial signs of status dysraphicus were frequent. These findings were confirmed by Coppez,[21] who states that status dysraphicus gives the key to the hitherto unknown etiology of Horner's syndrome.

It is not the dysplasias themselves, says Touraine [22] (1936), that are hereditary, but the common foundation, the status dysraphicus which, according to the individual subject, is revealed now by one and now by another of several manifestations, the ensemble of which deserves to be regarded as belonging to status dysraphicus.

Our search of the literature for familial cases of syringomyelia has brought to light some 30 instances of families that have been placed on record in which two or more individuals were afflicted. Among these are those of Bramann,[23] with symptoms in three brothers; of Goldbladt,[24] in a mother and daughter; of Price,[25] in which four generations shared in a group of similar dystrophies; of Krukowski,[26] in a father and daughter; of Karplus,[27] in a father and son; of Redlich,[28] in two brothers; of Wexberg,[29] in a father and son; of Barre and Reys,[30] in a brother and sister; of Kino,[31] in six members of a family group; of Riley,[17] in a mother and six children; of Schultze,[32] in three of a family; of Klippel and Feil,[33] in twin sisters, and of Goebbel and Runge,[34] who reported a family in which there had been 12 cases of symmetrical gangrene, six of which were fatal. In this family the males alone for three generations had this disease in the lower extremities, feet and toes, beginning at the age of eight to 10 years. Weitz [35] observed a case in identical twins. On the other hand, Stahle,[36] quoted by H. A. Riley, described twins 45 years of age, one of whom had a definite syringomyelia for about 19 years, whereas the other was quite well. He pointed out that, inasmuch as they were identical twins, the condition was not purely idiotypic.

Recently Van Epps and Kerr,[37] counting the individuals involved in these familial cases rather than the number of families, found a total of only 44 individuals on record as having familial cervico-thoracic syringomyelia, and in only four families did the number of such individuals exceed two. The lumbosacral group showed the greater familial tendency, embracing a total of 81 individual cases, 27 of which were subjects of their own report. Of these 27, 26 belonged in four families.

Barraquer and de Gispert [38] in 1936 reported 13 individuals in one family characterized apparently by a combination of cervico-thoracic and lumbosacral abnormalities. They think no other report has found 13 afflicted subjects in two generations, as here.

Few of the reports in English have discussed the so-called stigmata of degeneration on dysgenesis present in status dysraphicus. It seems there

is little difference in the patients reported by Riley as probable victims of status dysraphicus and those of Van Epps and Kerr who prefer the term lumbo-sacral syringomyelia. Smith's [39] six patients who had what he chose to call "a familial neurotrophic condition of the feet with anesthesia and loss of bone," closely resemble the patients as presented by Van Epps and Kerr, and our own patients.

From a practical point of view, there does not seem to be any particular reason why the two syndromes should be considered separately, unless one wishes to refer to status dysraphicus as a "microform of syringomyelia" (Passow), a disease more familial in tendency, exhibiting slower progress and consistent with a fairly active, useful life. The majority of reports of cases of true syringomyelia point out its slow, insidious progress. Curtius [40] says that the close connection of status dysraphicus with syringomyelia ought now to be generally realized. One can agree, he says, with those authors who wish to draw no line of demarcation between them. He regards it as "a matter of personal taste whether we will speak of a rudimentary lumbosacral syringomyelia or of a status dysraphicus (myelodysplasia)." The innumerable gradations pass insensibly from one to the other.

In 1928 De Vries [16] reported a case of unilateral clubfoot in a Chinese at 30 years of age. The condition appeared following an injury and exhibited trophic disturbances and infection. Spina bifida was present as was also enuresis. The temperature sense was lost in both feet and, to a lesser degree, the pain sense, affecting chiefly the first and second sacral dermatones. Pes cavus and trophic disturbances in both of the feet were present. De Vries called this a case of myelodysplasia (the term status dysraphicus had not yet found wide vogue). He points out that in extreme cases, in which glial proliferation is the main feature, the term lumbosacral syringomyelia may rightfully be used; but he believes that there are many transitional forms with slight neuroglia fiber production around the central canal in already existing congenitally deformed nervous tissue which do not fall into this category. He believes the term myelodysplasia (status dysraphicus) is applicable even when progressive symptoms do exist, provided they are largely of a trophic nature and do not give the typical progressive atrophies and sensory disturbances of syringomyelia.

Patients with status dysraphicus infrequently come to autopsy, so that not a great deal is known concerning the degree of pathologic involvement present. In the four patients whom Bremer autopsied, in whom there was clinical evidence of the condition, increase of glia tissue was found behind the central canal, which did not reach the posterior horns. One of these cases showed hydromyelia of the spinal cord. In this group the changes were for the most part confined to the cervical region.

None of our patients has come to autopsy, and we are unable to say to what degree the spinal cord is involved. We have been unable to follow our cases for a long period, but it would seem that the older members have shown the lack of progression which is so characteristic of true syringomyelia. The

deformities and loss of members seem to have followed complications brought about by infections. Two of the third generation appear to have more advanced neurological changes than those of the second generation, and the onset, according to the history, was at an earlier age. Lack of progression is our main clinical support for classifying these cases as status dysraphicus.

The similarity of the vasomotor and trophic disturbances that are such a prominent feature in many of these cases to those observed in Raynaud's disease naturally raises the question: Could they belong in the category of that syndrome? We have already pointed out that our attempts to precipitate these symptoms in one member of our group were not successful. Everything in Raynaud's disease points to a disorder of the vegetative nervous system and not of the central nervous system. The observations of many authors, however, show that the vasomotor disturbances which are sequels of nerve destruction can arouse symptoms very similar to those of Raynaud's disease. In such cases it is not difficult to demonstrate the destruction of the nerve as the cause of the phenomena. Cassirer [41] has pointed out that the degenerative muscular atrophy so characteristic of syringomyelia is not observed in Raynaud's syndrome, and that the extent of gangrene is greater in the former. In addition, the fact that in Raynaud's disease the vasomotor phenomena come in definite attacks, which abate to be repeated, and that these attacks are accompanied by pain, is a basis for differential diagnosis, since in syringomyelia and in status dysraphicus there is hypesthesia or even anesthesia, and the vasomotor and trophic symptoms are maintained at a static level. Cagel [42] thinks that Raynaud's gangrene can suggest syringomyelia only on superficial consideration, since the absence of muscular atrophy and the demonstrated sensibility disturbances with dissociated characteristics make a mistake hardly possible.

It was on such grounds as these that we felt safe in excluding Raynaud's disease from further consideration and found in status dysraphicus the complete explanation of all the symptoms exhibited by this series of subjects in our family group.

Conclusions

1. A family group is studied, embracing three generations, in which various individuals present degenerative constitutional signs, consisting of impaired circulation to the extremities, disturbance of sensation in the lower limbs and feet and, in a few members, similar disturbances of the hands.

2. Structural anomalies and so-called stigmata of degeneration were present in varying degree in nearly all the subjects examined.

3. The question is raised whether the condition afflicting this group represents a familial syringomyelia or should rather be regarded as the condition status dysraphicus.

4. The literature is reviewed and the nature of the two concepts examined.

5. Status dysraphicus is a thoroughly definite constitutional type, in which the developmental disturbance, consisting of a faulty closure of the

neural tube early in embryonic life, is readily transmitted to off-spring as a dominant characteristic.

6. The presence of status dysraphicus is revealed by the association of a typical group of pathologic characters, prominent among which are deformities of the feet with trophic and vasomotor disturbances and a dissociation of sensation, especially of heat and pain, such as are found in this family.

7. Syringomyelia, although producing similar disturbances, is regarded as being of a progressive type, owing to a gliosis of the spinal cord.

8. Not the dysplasias themselves, but their common foundation, the status dysraphicus, is revealed by these various heredo-degenerative manifestations, the ensemble of which should be regarded as belonging to status dysraphicus.

9. Status dysraphicus is related to syringomyelia quite closely, as a constitutional substratum for the latter, but is lacking in the progressive characters of genuine active syringomyelia.

10. In view of this lack of progression and the relatively static nature of the defect that marks this family, it is concluded that the disturbances are owing to the presence of a well-marked constitutional status dysraphicus.

11. The relation of status dysraphicus to other nervous diseases is still far from clear and requires further study.

Grateful acknowledgment is extended to Dr. Herbert Crockett, formerly Resident in Neuro-Surgery at the Los Angeles County General Hospital, for his kind coöperation and help in assisting with the records on one of the patients; to Dr. Lee Rice of San Antonio, Texas, who very kindly examined and sent reports on one of the patients; to Dr. Alfred Ackermann of Oklahoma City who helped with the translation of some of the literature and, finally, to many others including the patients themselves who have helped make this study possible.

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EOSINOPHILIA AND PNEUMONITIS IN CHRONIC BRUCELLOSIS; A REPORT OF TWO CASES *

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THE co-existence of extensive pneumonic infiltration, eosinophilia and immune reaction to *Brucella abortus* has been recently observed by us in two patients. The striking similarity of the clinical picture in these two cases suggests that the association of phenomena was not purely fortuitous, but that a common etiology exists. The syndrome was unfamiliar to us, and, so far as we can determine, has not hitherto been described. We believe it to be a manifestation of brucellosis, but only the recognition and study of similar cases will substantiate this assumption.

CASE REPORTS

Case 1. S. K. L., a 29-year-old housewife, first developed a fever of 99°–100° F. in 1934. It recurred intermittently until her admission to the gastrointestinal outpatient clinic of this hospital in February 1935. Physical examination was then essentially negative. Roentgen examination of the lungs was negative. Routine and differential blood counts were negative. After an afebrile period the fever recurred in March 1935 and intermittently throughout the following summer. Her general health was poor; she was underweight, and had a variety of ill-defined gastrointestinal complaints considered to be of nervous origin. During 1937 and 1938 she had five attacks of cystitis which subsided, as a rule, within a week. Urine cultures disclosed no organisms of significance. In December 1938 elevation of temperature to 102° F. in the evening occurred. She developed chills, malaise, a slight unproductive cough and marked tachypnea. She was admitted as a bed patient on December 16, 1938 (figure 1).

On physical examination the temperature was 101° F., pulse 112, respirations 36. She was dyspneic and slightly cyanosed but not seriously ill. The physical signs over the chest were few. Occasional râles were heard at both apices. The breath sounds were increased in intensity over the interscapular areas, but nowhere were signs of consolidation elicited. Examination of the heart was negative. The abdomen was slightly distended, and generalized tenderness was present. The physical examination was otherwise negative.

Roentgen examination of the chest (figure 2) showed extensive multiple bilateral exudative lesions extending to the peripheral pleura. The diagnosis was uncertain. The appearance of the shadows suggested atypical bronchopneumonia or a mycotic lesion rather than tuberculosis.

Blood examination disclosed a moderate anemia, leukocytosis of 16,600 and eosinophilia of 27 per cent. Blood, urine and sputum cultures were negative. Repeated stool examinations failed to reveal ova or parasites. A tuberculin test (.01 mg.) was negative.

Within two weeks distinct clinical improvement had occurred, although the temperature rose to 99° or 100° F. every evening and the eosinophilia increased to 40 per

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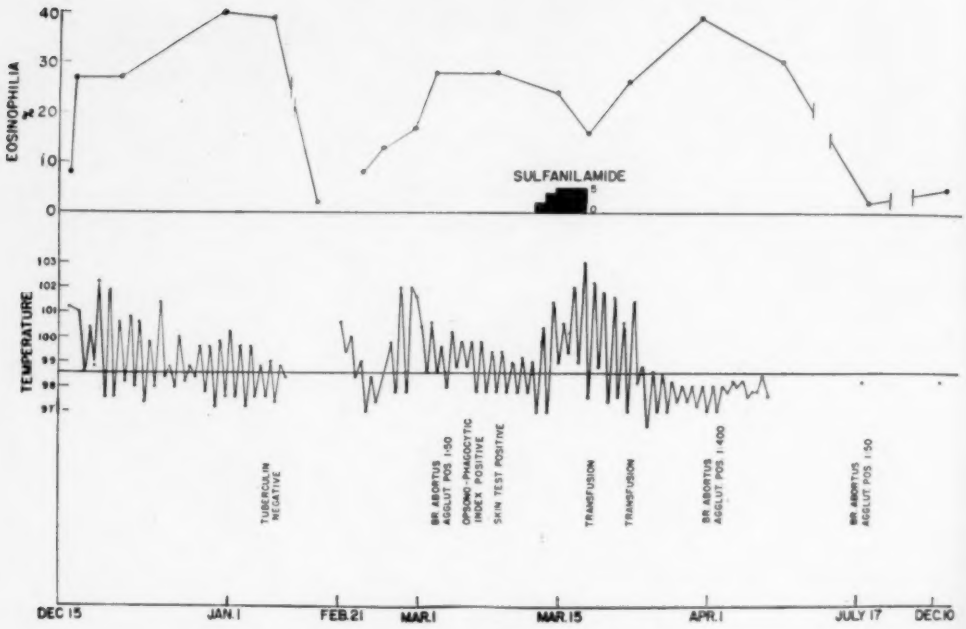
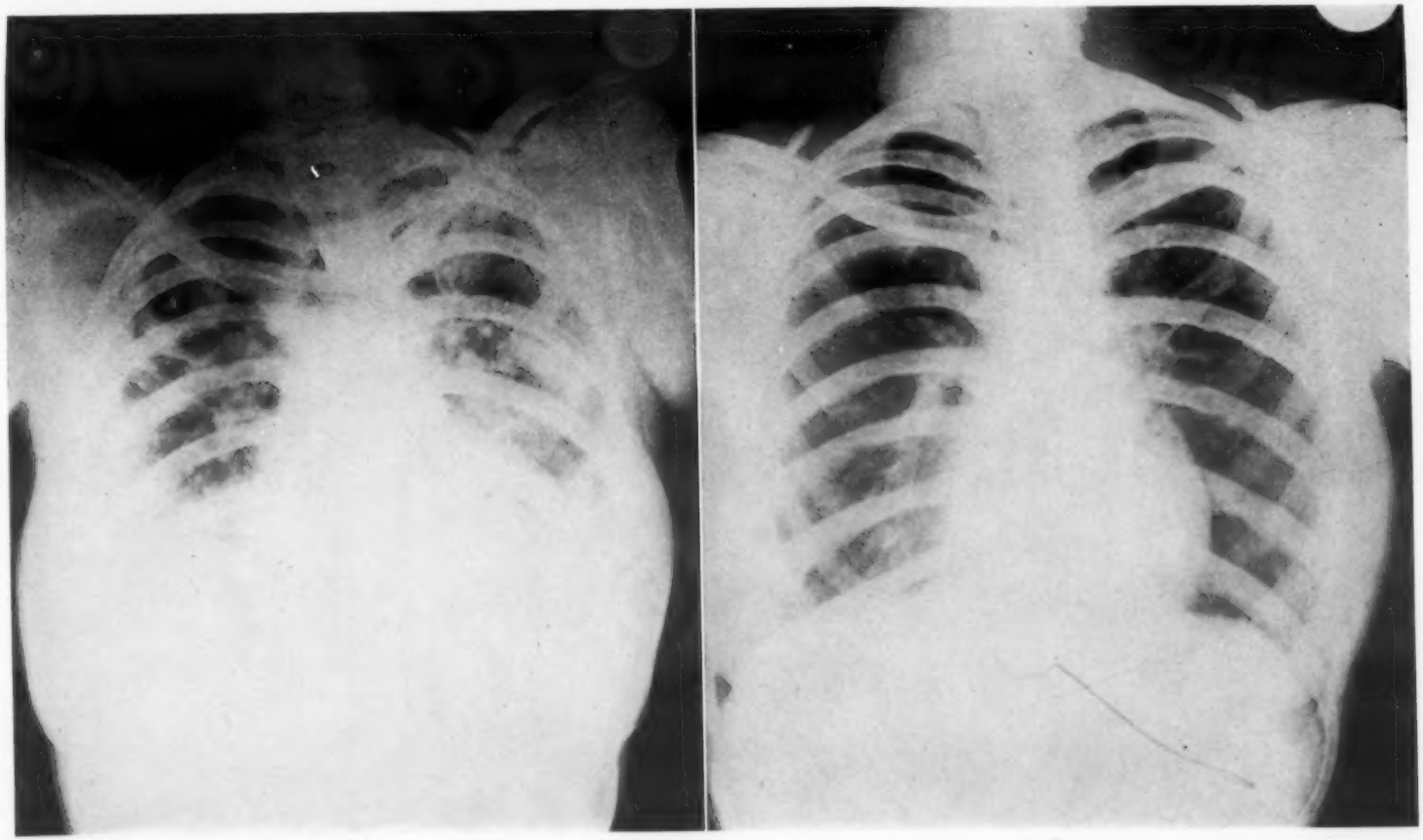


FIG. 1. Case 1. The temperature, the percentage of eosinophiles and the results of immunologic tests during and after the height of the disease.

cent. Examination of the chest was essentially negative and the roentgen appearance of the lungs was correspondingly improved. She was discharged from the hospital on January 6, 1939. By January 26 the lesions in the lungs were not visible in roentgenograms except in the left upper lobe. The leukocyte count was 10,500 of which only 2 per cent were eosinophiles.

In spite of the subsidence of the pneumonitis and eosinophilia she continued to have fever almost daily. By the second week in February it was apparent that the pneumonic process had recurred. Generalized râles and harshness of the breath sounds were again heard over the chest and the temperature reached 101° to 102° F. at night. She was, therefore, re-admitted to the hospital on February 21, 1939. Physical signs were essentially those of the first admission. Leukocytosis of 10,000 was found, and the eosinophile count rose within a week from 8 to 28 per cent. Serum gave a positive agglutination for *Brucella abortus* in a dilution of 1:50. In determining the opsonophagocytic index, 25 polymorphonuclear cells were examined; 18 showed moderate to marked phagocytosis of *Brucella abortus*, four contained a few organisms, and only three contained none. A skin test with Brucellergin was strongly positive. Attempts to culture the organism from blood, stools and urine were unsuccessful.

Sulfanilamide, 2 to 5 grams daily, was administered for five days. An explosive exacerbation in the pneumonitis occurred; râles were heard throughout the chest, the temperature rose to 103° F., dyspnea became intense, and the clinical condition was grave. The drug was discontinued and after oxygen therapy and repeated transfusions improvement occurred. Within two weeks after administration of the drug the temperature was normal and remained so for the duration of the illness. The evidence of pneumonitis disappeared both clinically and radiologically. After subsidence of the fever the *Brucella abortus* agglutination was positive in a dilution of 1:400. The eosinophilia persisted after recovery was otherwise complete. In July,



A *B*

FIG. 2. Case 1. Roentgenograms of the chest taken (*A*) on December 17, 1938, and (*B*) July 17, 1939.

1939, three months after discharge, the leukocyte count was 8,700 with 2 per cent of eosinophiles. On both physical and roentgen examination the chest was entirely normal (figure 2). The *Brucella abortus* agglutination was positive in a titre of 1:50. At the present (December 1939) recovery is apparently complete.

Case 2. Mrs. C. S., a 58-year-old Polish woman, was admitted to the medical wards of the University of Pennsylvania Hospital on December 2, 1938. She had developed chills, fever and a cough in June, 1938. She was then confined to bed for only two days, but had noticed dyspnea and a persistent productive cough for the remainder of the summer. In October 1938, she developed paresthesia in the right arm and hand, and to a lesser degree in the left arm. Pain was present in the right hand, arm, and right chest, especially on exposure to cold. She had lost 18 pounds (16 per cent of body weight) in the eight months prior to admission. Her appetite was poor. Repeated epistaxis had occurred in the month preceding hospitalization. For the preceding three and a half years she had lived on a farm and had consumed raw milk from uninspected cattle. Pork and beef from freshly killed animals had been ingested. The remainder of the history was negative.

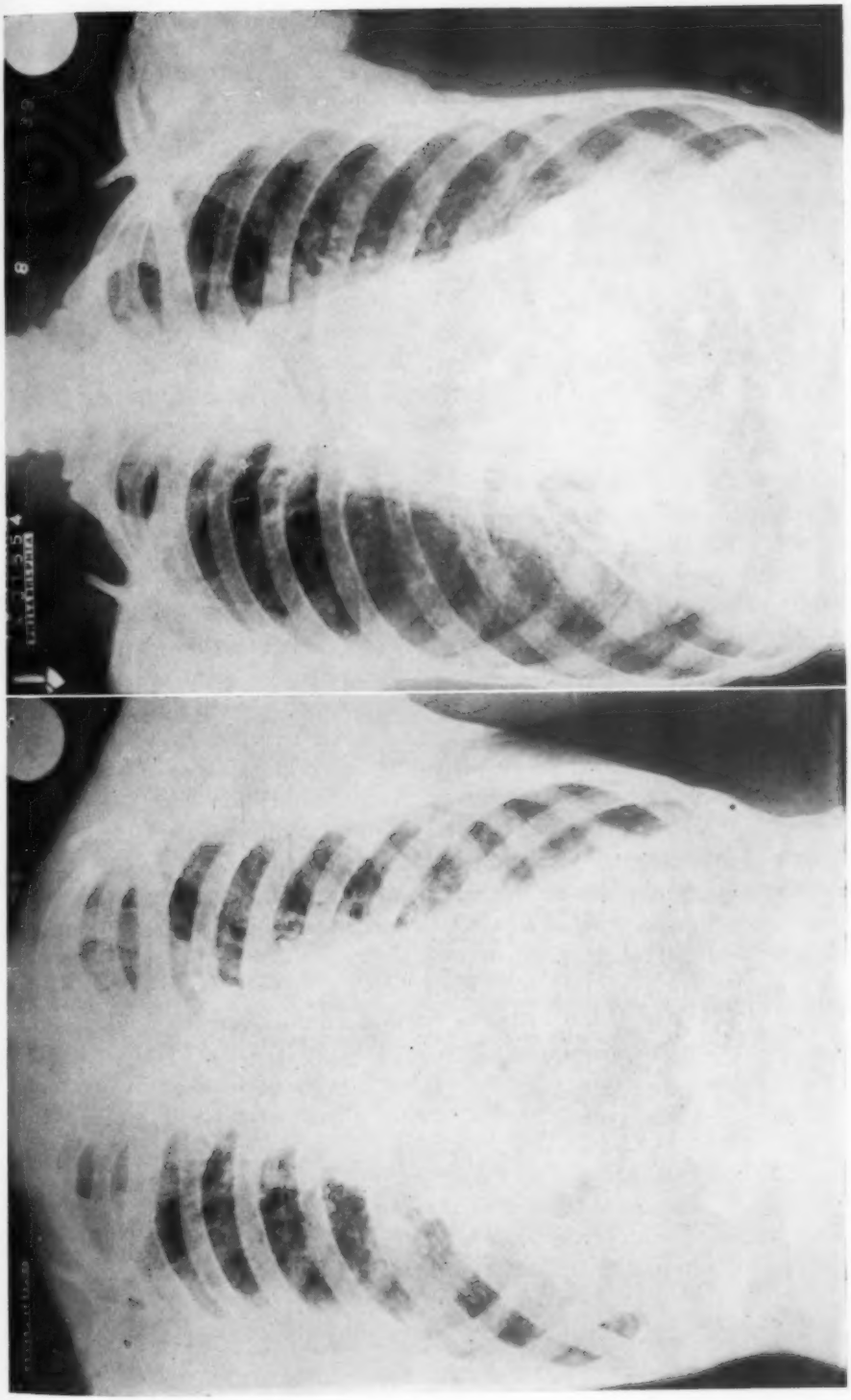
Physical examination revealed an emaciated middle-aged woman with normal temperature, pulse and respiration. Blood pressure was 138 mm. Hg systolic and 74 mm. diastolic. She had a non-productive cough. The skin was dry and inelastic. The muscles were generally wasted, but those of the right shoulder girdle and right arm were more atrophied than on the left side. Only a few teeth remained. The tongue was smooth and its edges were abnormally red. The tonsils were inflamed. Expansion of the chest was poor. Râles were heard over both lungs, but chiefly on the left side. Breath sounds were generally accentuated. The percussion note was not impaired. The heart was slightly enlarged on percussion. The abdomen was normal. Vibratory sense in the legs and feet was impaired, but tendon reflexes were preserved. A moderate grade of generalized arteriosclerosis was found.

Roentgenographic examination of the chest (figure 3) revealed moderate cardiac enlargement and marked increase in the hilar shadows. Multiple irregular lesions throughout both lung fields suggested a chronic inflammatory interstitial pneumonitis. The right costophrenic sulcus was obliterated.

Examination of the blood disclosed a marked eosinophilia. The leukocytes varied in number from 9,800 to 15,000, of which 29 to 42 per cent were eosinophiles. The other formed elements of the blood were normal. Other members of the family did not have eosinophilia. *Brucella abortus* agglutinins were strongly positive in the blood in a titre of 1:100, weakly positive in 1:200 dilution. A later test was strongly positive in a dilution of 1:200. Agglutinins for the typhoid-paratyphoid group were negative. Repeated sputum examinations and culture for tubercle bacilli were negative. Sputum culture yielded an abundant growth of a Friedländer-like organism not known to be pathogenic. Stools were repeatedly examined for ova and parasites with negative results. Skin tests to a variety of foods and to trichina antigen were negative. The fasting blood sugar was normal, but the sugar tolerance curve was of the diabetic type.

During hospitalization the pain in the right arm and hand, which constituted the chief complaint, was quickly controlled by analgesics and by application of heat. Temperature varied between 97° and 100.4° F. In spite of a high caloric, high vitamin diet the appetite remained poor, and weight loss of four pounds occurred in three weeks. The cough persisted, and the physical signs over the chest were essentially unchanged. She was discharged at her own request on December 23, 1938.

In March 1939, the patient was readmitted for further observation. In the interim she had lost five and a half pounds and had continued to cough. Pain in the right arm and hand was still present. Physical examination disclosed no new abnormalities. Eosinophilia of from 20 to 26 per cent was again observed. Leukocytes



A *B*

FIG. 3. Case 2. Roentgenograms of the chest taken (*A*) on March 28, 1939, and (*B*) August 1, 1939.

varied in number from 8,200 to 13,200. The opsonophagocytic test revealed that of 25 polymorphonuclear cells observed 18 showed marked and seven showed moderate phagocytosis of *Brucella abortus*. A skin test with Brucellergin was positive. Chest roentgenogram again showed pneumonitis. She was given palliative treatment and discharged on April 1. In the ensuing six months she gained 14 pounds, and became largely free of symptoms except for occasional cough. The leukocytosis and eosinophilia disappeared. In August, 1939 the *Brucella abortus* agglutination was positive in a titre of 1:800. The pulmonary signs observed by roentgen-ray had regressed (figure 3), and physical examination of the chest was negative.

Discussion

Both of these patients had diffuse pulmonary infiltration, fever, eosinophilia, and an immunologic reaction to *Brucella abortus*. In attempting to establish a common etiology the diagnosis of brucellosis deserves first consideration. The agglutination titre, while initially low, later rose to levels generally accepted as significant. The positive skin test and opsonophagocytic index added further evidence of immune response to *Brucella abortus*. These positive tests may merely indicate past infection rather than active brucellosis. However, lacking a typical clinical picture, the diagnosis usually rests on immunologic evidence alone, since culture of the organisms is uncommon. In case 1 the history of long standing recurrent fever is in harmony with a diagnosis of chronic brucellosis, although no known exposure to the organism had occurred; in case 2 exposure to infection seemed likely.

If the assumption is correct that the disease process was caused by infection by *Brucella abortus,* then the syndrome of fever, pulmonary infiltration and eosinophilia must be regarded as an unusual manifestation of brucellosis. Pulmonary abnormalities without eosinophilia have frequently been reported [1, 2, 3, 4] and may constitute the outstanding clinical feature of the disease. In many of the described cases, as in our own, the roentgenologic evidence of pulmonary disease was more striking than were the physical signs. Increase in the bronchovascular markings, marked hilum infiltration, and diffuse bronchopneumonic consolidation often resulting in extensive fibrosis have been frequently described. The lesions may simulate those of tuberculosis. Pulmonary abscess, pleural thickening and pleural effusions have occurred.

Eosinophilia, on the other hand, is not a usual observation in undulant fever. In several large series [5, 6, 7] it was not observed. Calder, Steen and Baker [8] observed eosinophilia of 5 per cent or over in one-fifth of their patients, but this is exceptional.

It is of interest to consider whether our cases are related to those of transient pulmonary infiltration and eosinophilia first described by Loeffler [9] in 1931. This syndrome, subsequently reported by a number of authors in Europe,[10, 11, 12, 13] is characterized by transitory and rapidly shifting infiltration of the lungs which usually disappears within three to eight days after a very benign clinical course with minimal symptoms and objective signs.

Eosinophilia usually ranges between 15 and 35 per cent but has exceeded 60 per cent in some instances. A marked seasonal incidence was observed by Loeffler, most of the cases occurring during the summer months. Although the exact etiology of the syndrome is in doubt, many of the cases were tuberculous. Most authors ascribe the lesion to an allergic or "hyperergic" response of pulmonary tissue to a generalized infection, although Wild and Loertscher [14] attributed it to migration of ascaris larvae through the lungs, and Engel [15] points to the similar clinical picture seen in China, thought to be due to sensitivity to privet. Agglutination tests for the brucella group were not reported in the cases referred to above, and it is impossible, therefore, to determine whether or not these organisms are concerned in the etiology of Loeffler's syndrome. Our cases differed from his in two main respects: the pulmonary lesion was by no means clinically insignificant, nor was it transitory in nature. Neither had any obvious evidence of allergy or of tuberculosis.

A final heterogeneous group of diseases is occasionally characterized by pneumonic infiltration and eosinophilia. Dobreff and Toscheff [16] have described eosinophilia of 30 to 59 per cent in a patient recovering from acute bronchopneumonia, and Gsell [9] states that 5 per cent of all patients recovering from acute pulmonary infection have eosinophilia of 10 per cent or over. Hodgkin's disease and periarteritis nodosa are known to produce bizarre clinical pictures having certain features in common with our cases. The apparent recovery of our patients tends to rule out these diagnostic possibilities. Minot and Rackemann [17] studied the incidence of respiratory abnormalities in trichinosis and report a number of instances in which the most significant initial features of the disease were pulmonary in origin. In our Case 2 negative skin tests with trichina antigen and a negative muscle biopsy were obtained. In Case 1 tests were not made, since pork was rarely included in the dietary.

Although the usual causes of eosinophilia have been excluded in our cases, we are cognizant of the fact that the evidences of allergy often escape detection. Whether a local tissue sensitivity to *Brucella abortus* or its products existed and ultimately resulted in an allergic or "hyperergic" pulmonary reaction remains a matter of speculation.

Summary

Two patients are described who presented a conspicuously similar clinical picture consisting of fever, pneumonitis, eosinophilia and immune response to *Brucella abortus*. Both made a good recovery. The disease process is regarded as a manifestation of chronic brucellosis. Although this etiologic possibility deserves first consideration, the exact cause of the syndrome remains undetermined.

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WHITHER? *

By JAMES ALEXANDER MILLER, F.A.C.P., *New York, N. Y.*

THE question which I have posed as the subject of my address this evening is on the lips or in the hearts of millions of the population of the world today.

It is obvious that I can have no intention of addressing myself to that vast audience. It is rather my purpose to suggest a searching of hearts and minds to our profession here in America and particularly to that portion of it which is represented in the Fellowship of the American College of Physicians. It was my thought that this Annual Convocation is especially timely for such introspection, inasmuch as upon this occasion a considerable body of young men are for the first time inducted into the privileges and responsibilities of Fellowship in the College.

If we are fruitfully to project our thoughts along a future path, it would seem wise first to indicate the point of departure. Where are we today?

Time allows for only a few observations.

We are in the full tide of a period of progress in knowledge, in science, and in medicine, such as history has never before known. American medicine is in the fore-front of this progress, and it is the great privilege of our generation to be participants in it.

Physicians engaged in research, in laboratory and clinic are constantly adding to our new knowledge. Practitioners are eagerly engaged in the exciting effort to put this knowledge into practical application.

More than elsewhere in the world, here in America the necessary tools are placed in our hands, in hospitals, in clinics, in laboratories, in equipment.

Educational opportunities for student and practitioner have never been greater, and you younger men are equipped in a manner unthought of by previous generations. Not only in diagnosis and treatment, but also in the prevention of disease, there have been great achievements, so that many dread scourges of the past are gone forever, and the fascinating prospect of the conquest of new similar worlds is ever before us.

These are a few of the bright lights on one side of the shield. What are some of the shadows to be detected upon the reverse?

Although the medical profession is giving a service of a higher quality than ever before, although the general health of our country measured in terms of general morbidity and mortality has been progressively improved, yet, there has probably never been a time when the medical profession has been under more widespread criticism. This anomalous situation is disheartening, and a constant source of wonder to us.

It may be worth our while to stop a moment and attempt to analyze it.

* Convocational Oration, American College of Physicians, Twenty-fifth Annual Session, Boston, Mass., April 23, 1941.

It is my impression that in spite of the inevitable development of specialism, which has modified the intimate personal relationship between physician and patient of former days that, individually, the warm feeling of understanding and affection for physicians as personal and family friends still persists.

It would appear that it is public feeling toward the profession as a whole which has changed.

In common with all other groups, we have become organized. Organizations are essentially impersonal. In some unfortunate manner, our organization has been manoeuvered into a defensive position. It is consequently felt that our virtues and our services of which we have always been subconsciously proud, something to be taken for granted, must now be vocalized.

Security, which nowadays appears to be more desirable than adventure, has become our important concern, to be militantly defended. We physicians, who have been notoriously complacent in such matters, being so very busy with our immediate tasks, are now thrown into the midst of the modern economic maelstrom.

The character of the services we render is in danger of being overlooked in the discussions over their compensation. Being individualists and conservative by nature and by training, more accustomed to quietly exercise our privileges for the benefit of others than to fight for our own rights, we are confused.

We frankly don't like it. Yet the rent must be paid, and that is not always easy.

A not unimportant factor in this situation is the more general diffusion of knowledge, or, at least, information, concerning matters medical. We physicians ourselves have fostered this change. Some of us can remember when the physician was a sort of high priest of mystery whose dogmatic pronouncements were delivered without explanation, to be accepted without question. This, to some extent, may have been faith healing, but to us now it smacks of quackery.

Intelligent coöperation is now the accepted basis of the relationship between physician and patient. Thus, to the other available sources of information, the physician adds his bit to the education of the laity in matters of health and disease. But this engenders among our patients a feeling of the right to criticize as well as to gratefully accept, and thus may the unwary physician be hoist by his own petard.

The press, the radio, and the medical advertiser carry the message still further and finally it reaches that guardian of a democratic people, the politician. Thus we are confronted with the greatest of modern bugaboos, State medicine. By this time, to be sure, enthusiasm may have outrun the truth but the alleged basis is, nevertheless, some sort of medical knowledge.

And why not? In these days, when the mid-Victorian veil is withdrawn from all secrets, whether personal or business, and the government, becom-

ing increasingly paternalistic in its concern for all of its people, reaches out into all other spheres of activity, why should medicine escape?

The answer is that it cannot, and probably should not, and the proper response from us should then be an intelligently insistent, "How?", rather than an indignant, "Why?".

Probably one of the most justifiable bases for criticism of present practice is the comparative neglect of social and preventive medicine.

In discussing "Trends of Medical Education" recently, Sigerist says: "We still need, more than ever, a scientific physician, well trained in laboratory and clinic. But we need more; a social physician who, conscious of developments, conscious of the social functions of medicine, considers himself in the service of society.

"The barriers between preventive and curative medicine must be broken down. This cannot be achieved by adding a few courses to the curriculum. A new attitude must be developed. The student must become interested in health, not only in disease. Clinical medicine must be taught differently from heretofore. Every case must be analyzed medically and socially as to the factors that have made it possible, and conclusions must be drawn as to how to prevent similar cases in the future."

I think that we must concede that these words paint a fairly accurate picture of the present, and are a challenge to the future.

It also must be recognized that prominent among the social considerations are the surrounding economic conditions, and that in the search for security, recognition of these social and community problems is essential to an understanding of our present situation, and that toward that end greater emphasis upon the prevention and social aspects of medicine appears indicated.

I have thus far endeavored to sketch a few of the important factors which influence medical practice in America today. With this background, I approach the main theme of my address.

In other words, where do we go from here?

In these confused times, no one could have the temerity to attempt a categorical answer to this far-reaching question. It is my purpose simply to consider certain angles of the problem as they apply particularly to medical men as suggestions for thought, rather than for a definite program of action.

John Buchan has recently expressed something of what is in my mind:

"We are condemned to fumble in these times, for the mist is too thick to see far down the road. But in all our uncertainty, we can have Cromwell's hope, 'To be a Seeker is to be of the best sect next to a Finder, and such an one shall every faithful Seeker be at the end."

This is particularly true for medicine, the constant eager zest for new knowledge. For those of us now well beyond undergraduate student days, we call it, *Continuing Education.*

This is no new idea to this College. It is in fact the foundation of its policies, the essence of its program, the very reason for its existence. Why then bother to emphasize so self-evident a fact? It is because it may be so taken for granted that in the midst of the present changing order and confusion of ideas, we may fail to hold to the realization that continued learning is the fundamental basis for progress in our profession.

Some of us who are older can look back and trace the subsequent careers of many who started with equal opportunities. Analyzing the outstanding characteristics of those who have achieved professional success, the capacity for sustained work and productive study appears paramount. When a practitioner ceases to be a student, his quality begins to shrivel and finally to die.

To those of you who are younger, the opportunities today are greater than ever before and the College offers many of them. Your election to fellowship is not a decoration for accomplishment, but rather a recognition of your potential capacity for achievement. It is a challenge, not a reward.

Recent developments in the National Defense Program, with the not unlikely possibilities of actual War, have materially affected the outlook of the medical profession. We may well ask what effect they will have upon our plans for continuing medical education.

In common with the rest of the country, we as physicians must and will meet our obligations which will involve many sacrifices, but the world situation demands that on no account should we allow ourselves to be diverted from our fundamental responsibility to maintain, even more than ever, a high quality of medical science.

In Europe, to which we owe so much of our background in culture and in science, the foundations of the old order are being ominously shaken. Universities are disrupted, libraries are being destroyed, orderly scientific research is at a standstill.

Together with all other social forces, medical science and medical research are being diverted solely toward the desperate problem of war and of defense. They are in a death grapple for existence with no possible constructive program for the future. In this country alone are orderly progress and independent scientific investigation possible. At no time in the world's history has a nation been so urgently called upon to keep aloft the torch of freedom and of science and in no field of endeavor is this demand more insistent than in medicine.

The President of the United States has said that America should be the arsenal for the Democracies. For us it must be more than that. America must also be the citadel of free and independent scientific thought if the present is to be saved and the future assured. This College is one of the important bastions of that citadel.

The present crisis may well tend to make continuing medical education more difficult, but actually it renders it even more essential. Disappointments may await us, both individually and collectively, but they can be overcome by

hard persistent effort, which they should enhance rather than discourage. We cannot, *must* not fail to meet this challenge.

At the close of a memorable address, a number of years ago, one of the greatest and most beloved leaders in American medicine, Dr. Edward Livingston Trudeau, left us this ringing message, which has even more meaning today than it had then.

"Let us not, therefore," he said, "quench the faith, nor turn from the vision, which, whether we own it or not, we carry, as Stevenson's lantern-bearers their lanterns, hidden from the outer world, and thus inspired, many will reach the goal. And if for most of us, our achievements must inevitably fall short of our ideals, if, when age and infirmity overtake us, 'we come not within sight of the castle of our dreams, nevertheless, all will be well with us.' For, as Stevenson tells us rightly, 'to travel hopefully is better than to arrive, and the true success is in labor.' "

In addition to continuing education to develop our knowledge, I would suggest that, in order to successfully meet the changing conditions which lie before us, we need the development of our powers of *adaptation*.

Trained in science we physicians are familiar with this term as a biological concept. Steeped in tradition, however, we have been slow to adopt it as an essential rule of conduct. We are conservatively skeptical of radical change, for we appreciate its dangers. Are we not in equal danger of failing to meet the challenge of changes which are already upon us and which we cannot ignore?

Our cloistered existence, which keeps us enveloped in the effort to attain knowledge and to put this knowledge into practical application, is outmoded and we must widen our horizon to include the larger field of social and community responsibility.

We cannot yet see clearly just what form it will take, but it is certain that the practice of medicine of tomorrow will be quite different from that of today or of yesterday.

The penetrating mind of Dr. George Vincent recognized this fact fifteen years ago.

In a brilliant address entitled "The Doctor and the Changing Order," he thus expressed himself;

" 'The old order changeth.' That is a law of life. To this changing order all, even doctors, must adapt themselves."

"This adaptation takes place, not through large comprehensive, elaborate schemes of reform but piecemeal, here and there, now and then, by happy chance, by trial and error, opportunistically, unconsciously."

"The larger the number of minds that see the trend of things the better the chances of gradual adjustment. So studies, comparisons of experience, experiments, demonstrations, discussion, all play a part and are welcomed."

"To sum up: It looks as if society means to insist upon a more efficient organization of medical service for all groups of people, upon distribution

of the costs of sickness over large numbers of families and individuals, and upon making prevention of disease a controlling purpose."

"Just how these ends will be gained only a very wise or a very foolish man would venture to predict. One thing seems fairly certain; in the end society will have its way."

This is a message from the past to which we may well still give heed today. It is to be noted how closely Dr. Vincent's ideas of fifteen years ago parallel those of Prof. Sigerist of today. These are not isolated expressions of opinion, but represent contemporary thought indicating definite trends of the times. We cannot ignore them. We must adapt ourselves to them.

It would appear from our discussion thus far, that the main challenge to our profession lies in the social and community problems which confront us.

I am reluctant to allow it to finish upon that note.

The character and influence of any group is the sum total of that possessed by the individuals which compose it. Faulty organization may hamper the possibilities for individual expression, but, by and large, no group can rise above the level of its individual components.

This brings us back again to individualism as a fundamental factor, and in this field we physicians are supposed to be shining examples. My point is that we, as individuals, must share in the responsibility of our profession as a whole. I am not at all sure that the criticisms that have been leveled at our profession, as a group, may not have some basis in a subtle change which has come over the attitude of many of us as individuals.

We hear much of such watchwords of modern social progress as security, rights, privileges. We hear all too little of that more fundamental requirement, obligation. Whatever excuse may be offered for this situation in other walks of life, it is not justified for a profession such as ours, which is dedicated primarily to the service of others.

There is certainly no such situation in the American College of Physicians. For a number of years it has been my privilege to be closely identified with this College, and during that time it has been one of my main professional interests. I know intimately not only your leaders, but also hundreds of our individual members, and I know that you are fired by high ideals and faithful to them in practice. Altogether, you constitute a grand group of men measured by any standard.

The present situation cries out for aggressive leadership. Where may we look for it with greater confidence than among the members of our own College?

As a College, we have very wisely, I think, adopted the policy of taking no active part in the sphere of social and economic medicine. But as individuals we are also members of the general medical profession, and it is to you as individuals that I am now addressing myself.

What constitutes leadership?

It is interesting and significant that General Wavell tells us that General

Allenby, who was his preceptor in the art of war, placed character as the outstanding qualification for a military leader. And General Wavell himself, in a recent interview, also places the possession of character at the very head of the requirements essential for a successful commander.

If this be true for leadership in war, one of whose main objects is the destruction of life, how much more should it be so for medicine, which is dedicated to its preservation.

I shall not attempt to define character, but we all recognize it implies moral and spiritual qualities, as well as intellectual capacity. It is also essentially an individual attribute.

This brings us back to the thesis that if we are to provide leadership, we must conserve and develop individual character.

The present confusion in the world is more than a clash of arms or a conflict of interests. It is a fight to the death for basic principles. We need to preserve not only our "way of life," a phrase which to me connotes too much of physical comfort and complacency, but still more, we need to preserve the intellectual freedom and spiritual values in life which have been achieved through centuries of conflict and which we have inherited from those who have gone before us.

This cannot be accomplished by waging successful war, but rather by developing that inward strength, our character. Indeed, failing to do this, we may well win the war and lose the peace.

Now, this development of character and the achievement of leadership cannot be achieved by letting each day take care of itself, with no thought of the morrow. It is no haphazard endeavor. It involves constant and conscious effort.

We are going through times and experiences which try men's souls. The problems and difficulties which confront us, as a profession, are overshadowed by the world crisis in which we, too, are involved. In the end it will be the moral and spiritual qualities which will decide the issue.

Here we are, favored members of the world's leading nation and of a profession which appears capable of achieving more than ever before in our history. Yet, we are confused, uncertain, frequently disappointed, and consequently often depressed. In times such as these it is easy to drift from our moorings and to lose sight of our customary guiding beacons.

We ask for leaders to rescue us from our difficulties. With our background and potentialities, should we not rather be preparing to lead both ourselves and others?

To do this we must be freed from the entanglements of our daily routine and take time to think of basic principles. We need to reorientate ourselves frequently.

How would it be if we, as a strong cohesive group of physicians, could make an earnest conscious effort to perfect our own characters in order to meet our present great responsibilities, both as physicians and as citizens?

How would it be if, in order to do that, we could make it a practice from time to time to withdraw from our busy engrossing lives, from the anxiety and the confusion about us, into the quiet of our secret inner selves and there each of us, with whatever spiritual assistance our particular philosophy provides, call it God or by any other name, regularly attempt to chart the course that we are following?

There, at intervals, quietly and alone, let us each one of himself, earnestly ask the solemn question, WHITHER?

CASE REPORTS

MASKED HYPERTHYROIDISM AS A CAUSE OF HEART DIEASE

(With Report of a Case With Long Standing Auricular Fibrillation Cured by Subtotal Thyroidectomy)*

By SAMUEL H. AVERBUCK, M.D., F.A.C.P., *New York, N. Y.*

ALTHOUGH masked hyperthyroidism as a cause of clinical heart disease has received well deserved emphasis by some authors (Lahey,[1] Levine,[2] Sturgis and Levine [3]) this subject has not received the adequate attention of internists. The thyroid factor, overshadowed by the signs and symptoms of heart failure, is extremely difficult to recognize, particularly in older individuals. In this older group of patients a diagnosis of the relatively more common arteriosclerotic coronary artery disease offers a ready explanatory etiology for the cardiac insufficiency. Its acceptance, however, automatically limits the therapeutic possibilities. In sharp contrast on the other hand is the opportunity for achieving a rapid and almost complete cure if thyroid hyperactivity can be identified as playing an important rôle in the cardiac breakdown. Although generally known to occur, there are few recorded examples of the miraculous transformation from chronically bed-ridden states of cardiac failure to comparatively normal health after subtotal thyroidectomy in this type of cardiac disease.

This presentation is offered as an example of how successful even long delayed subtotal thyroidectomy can be, illustrated by spontaneous resumption of normal sinus rhythm after operation in a patient who had had uninterrupted auricular fibrillation for four years. Furthermore, this case may serve as a text whereby the inherent diagnostic difficulties in this condition can be pointed out and the entire clinical picture reviewed.

CASE REPORT

W. M., a 65-year-old furniture salesman, came under observation in August 1938, complaining of weight loss. In the year past he had lost 20 pounds, with a total loss in four years of 40 pounds. Four years before, the patient had experienced attacks of paroxysmal tachycardia, but examination had revealed no cardiac abnormalities. Three and a half years previously his heart rhythm had become permanently irregular and a clinical diagnosis of auricular fibrillation had been confirmed by an electrocardiogram (figure 1*A*). His heart had continued to beat irregularly up to the present and he used digitalis sporadically. There was no dyspnea or palpitation except upon rather severe exertion, such as walking up grade or up steps. His appetite varied, but he was of the impression that his weight loss could not be explained by reduced food intake. There was a daily bowel movement but never diarrhea. He slept well and he could not recall excessive thirst, sweating, weakness, nervousness or excitability.

Thirty-two years previously a routine blood Wassermann test during an insurance examination was reported positive. For two years he received mercury by injection

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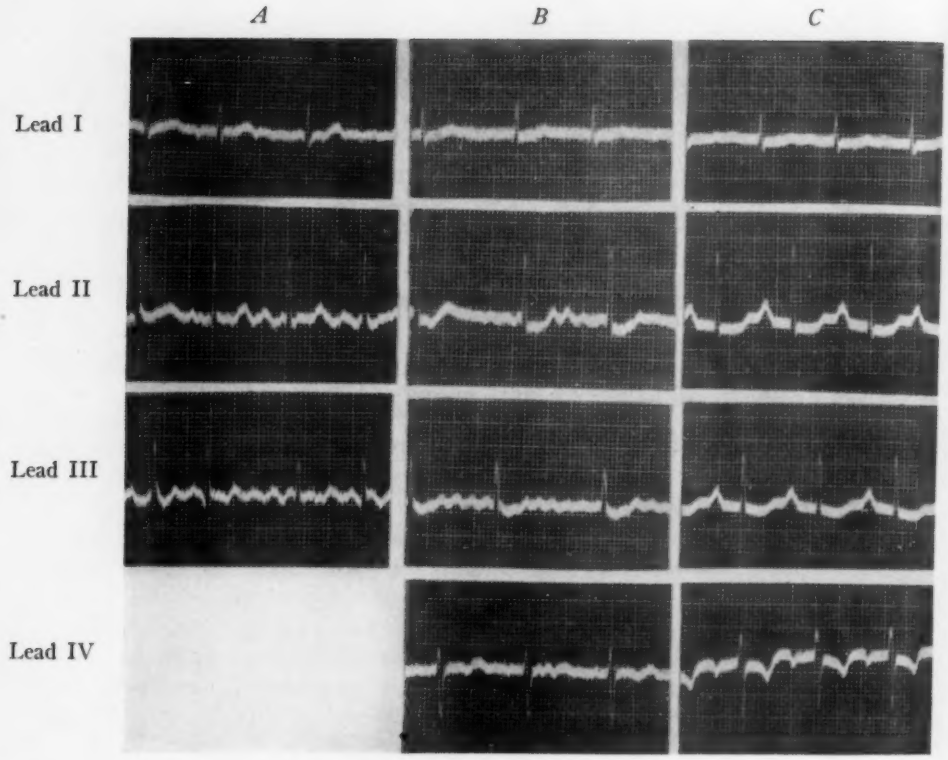

FIG. 1.

A. April 1935, showing auricular fibrillation.
B. April 1939, preoperatively, showing auricular fibrillation.
C. May 1939, ten days after subtotal thyroidectomy, showing normal sinus rhythm and changes due to digitalis.

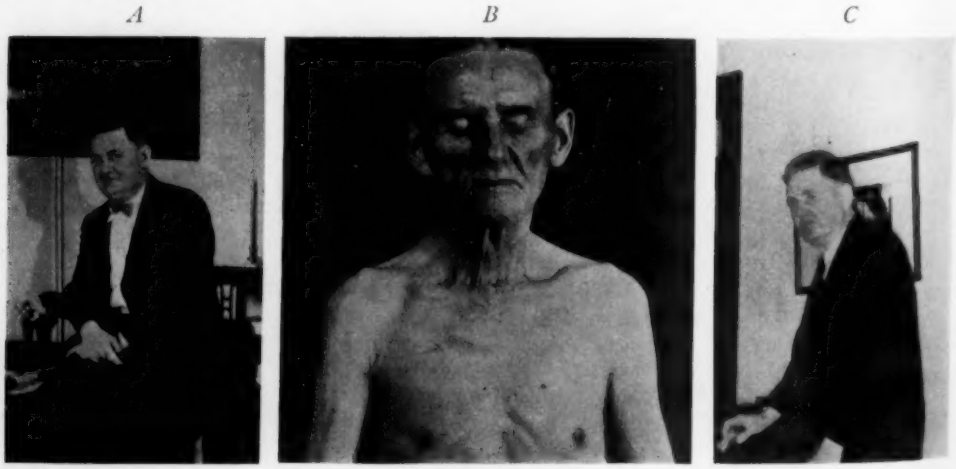

FIG. 2.

A. 1931, weight 185 lbs. (84 Kg.)
B. 1939, one week postoperative. Weight 106 lbs. (48.2 Kg.)
C. 1940, weight 160 lbs. (73 Kg.)

and the Wassermann reaction became negative and stayed so. Soon thereafter ulcerations appeared on the anterior and lateral surfaces of both legs. In the next 30 years these ulcerations disappeared and reappeared at varying intervals. No method of therapy, including varied ointments, ultraviolet light, or roentgen-ray was successful in curing the condition permanently. There were no other significant previous illnesses. He had been married and had one grown daughter. Tobacco and alcohol were used moderately.

Examination showed a well preserved man with moderate but definite emaciation (weight 134 pounds). His bodily movements were deliberate and somewhat slow, and he discussed his symptoms without any undue emotional color or overtone. There was no exophthalmos. The pupils reacted to light and accommodation. The gums were edentulous, and small normal tonsils were present. A small nut-sized nodule was palpable in the neck in the site of the right lateral lobe of the thyroid gland. The trachea was slightly deviated to the left. The lungs were clear. A large lipoma was present on the back over the right scapula.

The heart was not enlarged to percussion. The cardiac rhythm was completely irregular with a ventricular rate of 100 and a radial pulse rate of 90. A systolic murmur was heard at the apex, and the second aortic sound was louder than the second pulmonic sound. The systolic blood pressure was 120 and the diastolic 75 mm. of Hg.

The liver was enlarged two fingers below the costal margin. No other significant abdominal findings were present. The genitalia and prostate were normal. All peripheral pulses were patent. The skin was loose and thin and normally moist. Over both lower extremities were wide areas of superficially ulcerated weeping sores and scarred skin representing healed lesions. A slight tremor of the extended fingers was present. There was no edema anywhere. The neurological examination was normal.

Laboratory Data. The blood count was normal. The blood Wassermann reaction was negative. Fluoroscopy visualized a normal cardiac silhouette. The thoracic aorta was somewhat elongated, and there was a prominent knob on the aortic arch. The lungs were clear.

After the ventricular rate had been reduced to 80 and the pulse deficit to two with digitalis, the basal metabolic rate was determined. The rate was plus 16 per cent (+16) on two occasions. Electrocardiogram (figure 1*B*) showed auricular fibrillation, depressed RT segments in the standard leads and a diphasic T_4. The segment changes were ascribed to the effect of digitalis.

The steady weight loss, the thyroid nodule, and the tremor of the outstretched fingers in combination with the auricular fibrillation, in spite of the comparatively normal metabolic rate, suggested the diagnosis of masked hyperthyroidism with cardiac manifestations, and subtotal thyroidectomy was proposed.

In anticipation of operation iodine therapy was begun. Ten minims of Lugol's iodine solution were given twice daily and a maintenance daily dose of three grains of digitalis leaf was continued. The patient decided to defer operation and discontinued the iodine for varying periods of time, resuming it again at will. He noted that his weight remained stationary while he took iodine. The cardiac rhythm was controlled with digitalis but remained completely irregular. The hepatomegaly disappeared.

He finally entered The Mount Sinai Hospital for operation in April 1939. The preoperative metabolic rate was plus 13 per cent (+13) and his weight was 123 pounds, a further loss of 11 pounds in eight months in spite of some medical therapy.

Under avertin and ethylene anesthesia a bilateral subtotal thyroidectomy was performed. The thyroid gland was found to be diffusely enlarged two and one half times normal size. It was situated posteriorly very deep in the neck where it could not have been palpable clinically. The trachea was deviated to the left.

For a few days postoperatively the patient did poorly, becoming very lethargic and apathetic. There was disorientation at times, and the pulse became extremely weak. Iodine was stopped, and stimulation with caffeine begun. This was effective, and

from that time convalescence was progressive. On the tenth postoperative day, the cardiac rhythm became regular with a rate of 85 (figure 1*C*). Digitalis was discontinued. Two weeks later the patient left the hospital.

Examination of the removed tissue was reported as follows. "On section these two thyroid lobes are similar in character and made up of numerous smaller distinct and separate nodes which are well encapsulated, alternately hemorrhagic and cellular, brown in color, containing a good deal of colloid and surrounded at the periphery by compressed relatively normal fleshy appearing thyroid tissue. The isthmus likewise contains a number of these nodules. Diagnosis: Macro- and microfollicular colloid adenoma."

In August 1939, four months after operation, the patient was examined. He weighed 148 pounds, a gain of 25 pounds, since the operation. His cardiac rhythm was regular with rate 88. The chronic ulcerated condition of his extremities had healed a few weeks after his discharge from the hospital and was still completely healed. There were no cardiac symptoms, and the patient felt completely normal.

In May 1940, the patient wrote from another city where he was living, "Feeling fine. Weight 160 pounds. Heart regular. Enclosing recent picture."

In May 1941 he reported by mail that his heart was regular, that he was maintaining his weight and that he was feeling very well.

Comment

In the case presented it is apparent that there were very few diagnostic aids. Aside from the auricular fibrillation which one so frequently encounters as evidence of coronary artery sclerosis in this age group, the only symptom which suggested a thyroid element was the steady weight loss over a period of years in spite of definite attention to food intake. Other clinical features which took on significance in retrospect were a very slight tremor of the extended fingers and a small thyroid nodule which could barely be palpated. The metabolic rate was minimally elevated (+ 16 per cent) and the fibrillation could be successfully controlled with the customary amounts of digitalis, features which were of no aid in establishing a diagnosis. With iodotherapy there was a retardation of the rate of weight loss but for the short period of time this drug was being administered no definite conclusions were warranted. Each of the foregoing manifestations alone could not be considered diagnostically significant, but in combination they produced a clinical syndrome that was fairly definite and that justified subtotal thyroidectomy.

Perhaps best proof of the eventual correctness of the diagnosis was the response to the surgical ablation of the thyroid gland. The spontaneous restoration of normal sinus rhythm 10 days after operation could occur in no other disease. Furthermore, the great weight gain immediately after operation and the disappearance of all signs and symptoms of cardiac insufficiency were additional proofs. An unexpected benefit, the rapid and permanent healing of the chronic leg ulcers, may be considered a sign of the metabolic changes induced in all the tissues of this patient by subtotal thyroidectomy.

The Auricular Fibrillation

The patient presented one of the most characteristic cardiac manifestations of masked hyperthyroidism, i.e., auricular fibrillation. This was maintained un-

interruptedly for four years from April 1935 to May 1939. It was controlled easily with average doses of digitalis and was accompanied by varying degrees of myocardial insufficiency. The arrhythmia disappeared spontaneously 10 days after subtotal thyroidectomy, and the cardiac rhythm has remained normal since then, one year ago. Search of the literature has failed to find mention of a similar instance. In a series of 108 cases of auricular fibrillation in Graves' disease Barker, Bohning, and Wilson [4] found an average duration of the arrhythmia of one year in the adenomatous group and 0.8 year in the exophthalmic group. These authors state that auricular fibrillation may appear before a significant elevation of the metabolic rate occurs. They observed spontaneous return to normal sinus rhythm in 53 per cent (28 cases) of the 53 who were operated upon. Anderson [5] saw 32 per cent of 75 cases operated upon develop regular sinus rhythm. One case in this series had had auricular fibrillation for 20 years, but no indication is given in his paper whether or not his patient was included in the operated group. Hamilton [6] reports an instance of auricular fibrillation for 12 years which, however, was not restored to normal sinus rhythm after thyroidectomy.

Ernstene [7] likewise observed normal sinus rhythm reëstablished in one-third of thyroidectomized patients with persistent fibrillation. Burch [8] reports an instance of auricular fibrillation of 22 months' duration, but his patient did not have Graves' disease. A bibliography of similar cases may be found appended to his paper.

Of particular interest is the spontaneous resumption of normal rhythm after subtotal thyroidectomy. Now it is generally agreed that hyperthyroidism does not produce degenerative myocardial changes and that in an otherwise normal heart Graves' disease does not produce permanent heart muscle change. Thomas [9] in a review of this subject states "if the hyperthyroidism is successfully terminated by subtotal thyroidectomy and adequate postoperative treatment is observed, the heart will sooner or later return to the state in which it was found at the beginning of the hyperthyroidism, allowing only for changes which would have occurred in a similar length of time under other conditions." Careful pathological studies have not confirmed earlier theories about changes in thyroid hearts. McEachern and Rake [10] after an exhaustive examination of all the hearts of patients dying with hyperthyroidism at the Johns Hopkins Hospital concluded that no pronounced pathological change is produced in the heart of hyperthyroidism. With the removal of a thyroid factor that had caused a change in the cardiac rhythm for four years in this patient, the rhythm became normal. This would indicate quite emphatically that the thyroid factor had its effect only when present and that it had not caused any persisting alterations. Furthermore, there is in this case the suggestion that operation offers real chance of improvement in patients who have had the condition for many years and in those in whom the condition is not recognized until late.

The Clinical Picture of Masked Hyperthyroidism Associated with Heart Disease

Masked hyperthyroidism as a cause of heart failure is relatively infrequent but, because of its amenability to therapy, extremely important to recognize. The cardinal signs of hyperthyroidism—an enlarged gland, tremor and exophthalmos—are usually absent, and there is often little to suggest that the pre-

senting picture of congestive heart failure with or without a cardiac arrhythmia has a thyroid basis. It must be remembered that the clinical picture is the result of an atypical or extremely mild hyperthyroidism usually with adenomata, acting on the heart for many years. Awareness of the existence of such cases will enhance diagnostic acumen and increase the frequency with which these patients are identified.

The syndrome occurs most frequently in women after middle life. Most often these individuals appear apathetic instead of hyperkinetic although there may be a noticeable alertness or rapidity in the manner in which they perform simple acts. Exophthalmos is extremely rare, but an ocular stare is not uncommon. The significance of the eye signs may be difficult to determine because of coexistent moderate to severe degrees of emaciation. The emaciation is caused by weight loss which may have continued slowly over a period of years in spite of adequate food intake and restricted activity. The edema resulting from heart failure may restore some of the body weight, but if sought for, a history of inexplicable but definite weight loss at some time is commonly obtainable. Rarely is this symptom absent. Fine tremor of the extended fingers may be observed, but too often this sign is not present. Pigmentation of the skin occurs. The thyroid gland may be normal to palpation, perhaps with a diffuse increased hardness. Diligent search will disclose small thyroid nodules in some cases. Other symptoms frequently associated with classical Graves' disease such as intolerance to heat, flushed moist skin, diarrhea, and general nervousness are not usual. The metabolic rate may be elevated, with figures surprisingly higher than the clinical impression would justify. Very often, however, there is only a moderate elevation in the metabolic rate from 10 to 20 per cent, and occasionally the metabolic rate is normal.

Because of the indistinct nature of the hyperthyroid symptoms and signs, the cardiac manifestations in masked hyperthyroidism dominate the clinical picture. To be mentioned in passing are simple tachycardia, with or without premature contractions, and paroxysmal tachycardia, cardiac manifestations which so often characterize cases of outspoken Graves' disease. Such variations in cardiac rate and rhythm do not occur frequently in masked hyperthyroidism.

More common and diagnostically significant is paroxysmal or maintained auricular fibrillation. This cardiac arrhythmia may be the only clue to the nature of the heart affection and point the way to the detection of the thyroid element underlying the clinical picture. Another lead to the etiology of the fibrillation is the great difficulty encountered in controlling the arrhythmia either intermittently or persistently. In such cases hyperthyroidism must be excluded, whether or not there is coexistent heart disease of another etiology.

Dyspnea, edema, and other signs of congestive failure may occur in long neglected, far advanced cases, but more generally these signs are determined by the extent of the underlying cardiac impairment upon which the hyperthyroidism acts as a precipitating and intensifying component. Dyspnea dissociated from paroxysmal arrhythmias is not common. Precordial pain may accompany the onset of paroxysmal fibrillation, or angina pectoris may be present independent of the arrhythmia.

In some instances the heart sounds possess an overacting quality which is so well heard in thyroid hearts with regular rhythm. Usually auscultation gives no special information aside from the arrhythmia although some authors describe a

forcible, short sudden apex beat, and systolic or pseudo-presystolic apical murmurs similar to those heard in active Graves' disease. Diastolic murmurs are not present and their absence helps to exclude frequently misdiagnosed mitral stenosis. The systolic blood pressure may be elevated. Fluoroscopic findings are determined by the duration of the hyperthyroidism. The older the case and the more extensive the involvement by arteriosclerosis or other types of heart disease, the greater the degree of cardiac enlargement. There is no characteristic cardiac contour in masked hyperthyroidism. The electrocardiogram confirms the totally irregular rhythm, but it is otherwise not remarkable.

In summary, the occurrence of auricular fibrillation, with or without cardiac failure in a middle aged patient who presents a definite degree of emaciation or a history of weight loss, presenting some of the clinical features enumerated above, should stimulate careful search for a hidden hyperthyroidism. The usual signs of hyperthyroidism, struma, exophthalmos, tremor or elevated metabolic rate may not exist or if present, may be of insignificant degree. Organic heart disease of another etiology may coexist, but of itself is not the cause of the cardiac insufficiency or arrhythmia.

The outlook for this group of cases in spite of the fact that the patients are older and have usually had their disease for a long time is as favorable as for patients with active hyperthyroidism. From the standpoint of the cardiologist they afford an unusual opportunity for the radical removal of the cause of heart disease, an opportunity as desirable as it is rare. One must not be deterred by the apparent hopelessness of the condition in which these patients are found, or by the poor surgical risk they appear to present. Nothing can be expected from medical therapy and although hazardous, surgery should be undertaken in every case because of the excellent hope of real improvement and often of complete cure (Lahey [11]). Of prime importance in the determination of the success or failure of the operation is the preoperative medical preparation. The signs of myocardial insufficiency must be reduced to a minimum by the use of the usual cardiotherapeutic measures, i.e., digitalis, diuretics, limitation of salt and fluid intake, rest and sedatives. If an arrhythmia such as fibrillation or more rarely flutter exists, it must be brought under maximum control with digitalis. Lugolization is accomplished in the same way as in the now routine preoperative treatment of Graves' disease. Some experience is required to select the most beneficial time for operation, and the active coöperation of surgeon and cardiologist produce best results. Lahey suggests that the operation always should be performed in two stages. Ethylene after preliminary narcosis with avertin is a favorable combination of anesthetics.

These cases may pursue an individual postoperative course also. If unfavorable, it is characterized by increasing apathy and preterminal coma, so different from the delirium and hyperactivity attending the death of a patient with obvious hyperthyroidism. Iodine should be discontinued after operation, and stimulation with caffeine or coramine begun when indicated.

Summary

A case of masked hyperthyroidism with auricular fibrillation of four years' duration is described. Spontaneous resumption of normal sinus rhythm occurred 10 days after subtotal thyroidectomy.

The clinical syndrome of cardiac disease associated with masked hyperthyroidism is reviewed and discussed.

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GONOCOCCUS BACTEREMIA WITH JOINT AND SKIN MANIFESTATIONS; A CASE REPORT *

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THE following case is reported because it represents a syndrome characterized by fever, joint pains and rash typical of certain gonococcal bacteremias. It was undiagnosed before the laboratory isolated the organism from the blood stream, but it is probable that the case could have been diagnosed from the clinical course alone and proper therapy started at once. Several similar cases have been reported by Wheeler and Cornell,[8] Rubenstone,[7] Cabot,[1] Filler,[3] and Keil.[5] The following case report is identical in many ways to these reported cases.

CASE REPORT

A 20-year-old white female was admitted to the University of Wisconsin Student Infirmary on December 23, 1939 because of a chief complaint of "sore joints." She had felt well until December 20 when she developed multiple joint pains, stiffness, generalized muscle soreness and a temperature of 99.4° F. The following day the temperature was 101° F. accompanied by general malaise and increased pain involving the fingers, wrists, shoulders and knees.

The history by systems revealed nothing of significance.

* Received for publication July 21, 1941.

The past medical history was of interest because, following a slight cold in January 1937, the patient was hospitalized due to pain in the shoulders, wrists and fingers. At that time the only pertinent findings were a soft systolic murmur along the left sternal border disappearing with deep inspiration, and a rapid sedimentation rate. Numerous electrocardiograms were normal except on one occasion when the P–R interval was 0.21 second. The impression was that this may have been a mild rheumatic fever although later cardiac examinations revealed no pathology. Occasional joint pains persisted until the present illness.

The physical examination revealed a well developed and nourished patient not acutely ill. There was tenderness of the left hand, wrist and shoulder, and of the right knee, but no redness or swelling was present. There were bilateral diseased tonsil tags. The cardiac examination revealed a soft blowing systolic murmur along the left sternal border similar to that heard upon previous examinations. The pulse was 88, blood pressure 120 mm. Hg systolic and 82 mm. diastolic, and the temperature 98° F. The liver and spleen were not palpable. The leukocyte count was 8,650 with a normal differential, the sedimentation rate was 18 mm. and the electrocardiogram was normal. There was a daily febrile reaction of 99.2° F. but the pains rapidly subsided and on December 27 the patient had no complaints. However, on this date it was observed that the white cell count had risen to 13,850 with 74 per cent neutrophiles.

On the afternoon of December 28 there was stiffness of the joints. On the morning of December 29, nine days after the onset of the illness, there were chills, "pain all over the body" and a temperature of 104.2° F. The physical examination showed an acutely ill and uncomfortable patient with exquisite tenderness over the dorsal spine and both shoulder joints. The white cell count was 21,900 with 85 per cent neutrophiles. By evening the temperature started to fall. At this time a few discrete reddish-purple maculopapular lesions about 0.3 mm. in diameter appeared over the extensor surface of the forearms, hands, legs and chest. The following morning these had a hyperemic base with a small vesicle in the center. Several of the vesicles had a hemorrhagic appearance. The patient then recalled having had a similar rash with the first attack of fever and joint pains, December 23, 1939.

The above symptoms subsided within 24 hours. The white cell count fell to 11,300 and there was apparent convalescence until January 4, six days after the exacerbation of symptoms, when there was another attack similar to that described above. A maculopapular eruption again appeared, this time on the chest, back and arms. The lesions were identical to those noted previously. A few later developed vesicles. There was some swelling of the fingers of the left hand, the first occasion on which swelling was present. The temperature reached 102.4° F. and the white cell count 24,550.

On January 8, four days after this attack, there were gas pains and excruciating pain in the right lower quadrant and right chest associated with vomiting and several liquid stools. The patient appeared very ill, obviously nauseated and in great pain. Her temperature was 102.4° F., the white cell count 43,450 with 93 per cent neutrophiles, but no physical findings suggested pathology in the chest or abdomen.

Because of the episode of fever, joint pains, and the simultaneous appearance of the rash described, blood cultures were taken with the first febrile reaction December 29. These showed no growth in 24 hours but by January 4 a gram negative diplococcus was isolated which was later identified as the gonococcus. The patient denied exposure to gonorrhea. A pelvic examination revealed a slight urethritis but no pelvic pathology. Smears from the urethra were positive for gonococci, but smears from the cervix and vagina were negative for this organism.

On January 8 it was felt that the diagnosis in this case was gonococcal bacteremia. The patient was acutely ill and too nauseated to be given oral medication. At 12:45

p.m. she was given 3 grams of Promin intravenously. By 4:00 p.m. the temperature had dropped to 99.6° F. and all gastrointestinal symptoms had subsided. The following morning sulfanilamide grains 80 daily was started. This was given for two days followed by 60 grains daily for three days and 40 grains daily for six days. The temperature remained normal and the patient was free from all symptoms after the second day of medication. Repeated smears and blood cultures were negative.

This individual has been followed for 18 months. There has never been an exacerbation of her symptoms nor has she had a recurrence of the muscle pains noted during the two years previous to her illness. Repeated cervical, vaginal and urethral smears have been negative for the gonococcus.

Discussion

Typically, patients with this syndrome have a remittent fever although the course is not so characteristic as the double quotidian temperature frequently seen in gonococcal endocarditis. This patient had a febrile reaction about every six days (figure 1), suggesting the possibility that the fever caused a tem-

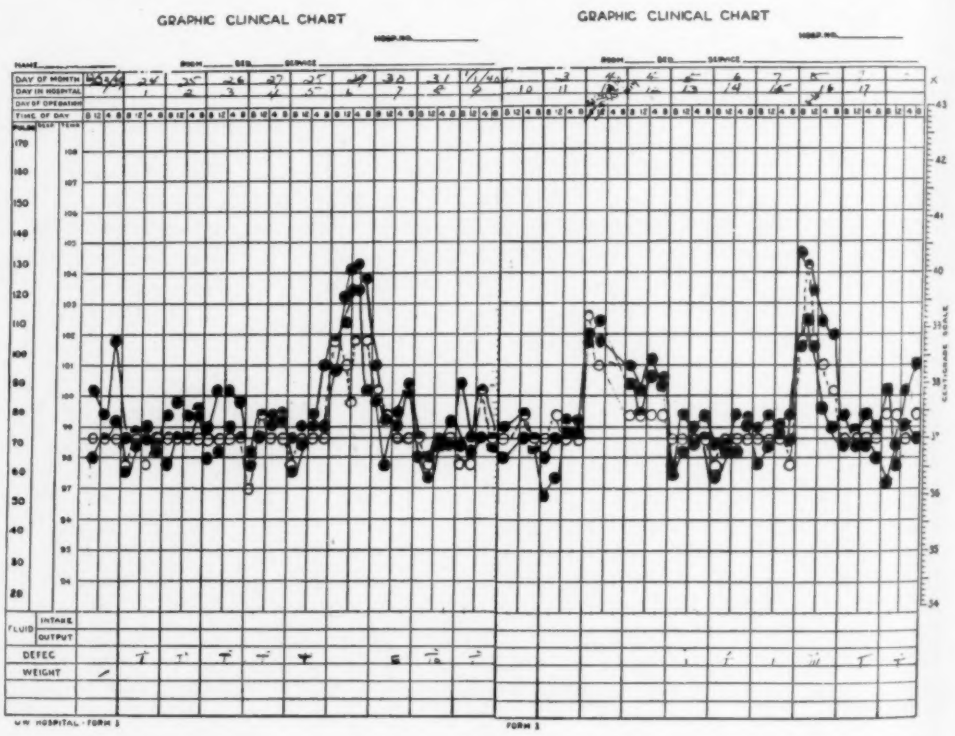

Fig. 1.

porary sterilization of the blood stream. However, sufficient blood cultures were not taken to establish this fact.

In these cases joint pains may or may not be localized and frequently there is swelling with local redness of the joints. Keil [5] reports two cases which began with a sore throat so it is not surprising that the condition is frequently

mistaken for rheumatic fever. However, it fails to respond to salicylates and the electrocardiogram shows no findings characteristic of rheumatic fever. This patient received large doses of salicylates without relief. Repeated electrocardiograms taken during her illness were normal.

The skin lesion is the characteristic feature. Gonococcal eruptions are classified as: (1) Erythemas, (2) urticaria and nodosal lesions, (3) hemorrhagic and bullous lesions, and (4) hyperkeratoses.[5] In 1938 Keil [5] described five cases of gonococcal bacteremia without endocarditis and with a characteristic hemorrhagic vesiculopustular lesion. He stated that these lesions are discrete, are not extensive in distribution and that they have a tendency to occur in crops, especially during a febrile period. They start as "an erythematous macule that acquires a central vesicle or pustule." [5] Not infrequently a hemorrhage occurs in the center of the lesion and occasionally organisms are present in the vesicle. This case had erythematous lesions, many of which became vesicular, a few later developing hemorrhagic centers. The lesions appeared in crops with each febrile reaction.

The patient showed no evidence of endocarditis nor did those cases described by Keil.[5] Davis [2] has stated that in gonococcal septicemia cutaneous lesions usually indicate an infection of the blood stream in the absence of a complicating endocarditis. Patients with a gonococcal bacteremia without endocarditis have a good prognosis. The course may be prolonged, in some perhaps for years. Because of repeated denials of exposure it is impossible to state when our patient developed her original infection. It is interesting that she had atypical joint pains for two years without a true endocarditis and that she has had no joint pains in the 18 months following the acute illness. Whether she had had an old gonococcal infection with a recent exacerbation is unknown. Frequently the local focus in these cases is never found and no history is obtained to indicate a gonococcus infection.

In this individual the response to the sulfonamides was spectacular. Within three hours after the intravenous Promin the patient was afebrile and asymptomatic. There has never been a recurrence. There was delay in giving the drug because of the time required to isolate the organism from the blood stream and identify it. Unfortunately, in many of these cases the organism is not isolated. In the latter group it is important to recognize the syndrome of joint pains, fever and vesicular rash so that therapy may be instituted.

Summary

A case of gonococcal bacteremia characterized by fever, joint manifestations and a vesicular dermatitis is presented and discussed. The response to the sulfonamides was immediate.

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EDITORIAL

LYMPHOCYTIC CHORIOMENINGITIS AS A SYSTEMIC DISEASE

CASES presenting the clinical syndrome later designated as lymphocytic choriomeningitis were first described by Wallgren (1935) under the term acute aseptic meningitis. These cases presented the picture of an acute febrile infection accompanied by manifestations of meningeal irritation. They all recovered after a short illness without sequelae. The cerebrospinal fluid showed a well marked increase in lymphocytes but yielded sterile cultures. Recognized conditions which may cause similar reactions in the cerebrospinal fluid, such as tuberculous meningitis or poliomyelitis, could be excluded.

In 1935 Rivers and Scott [1] isolated from the cerebrospinal fluid of two such cases a filtrable virus which has since been known as the virus of lymphocytic choriomeningitis. This was quickly found to be identical with two strains of virus previously isolated: one by Armstrong and Lillie (1934) from a monkey, the other by Traub [2] (1935) from a colony of white mice. Since that time 35 cases of the disease have been reported [3, 4] which have been proved to be caused by this virus. These 35, however, make up less than a third of the cases designated as acute septic meningitis which have been adequately investigated. Some of the other cases have yielded viruses antigenically different, but in many the cause could not be determined.

Although the small number of proved cases suggests that the disease is rare, it has been found widely distributed in the United States. The virus has been reported from England, France and Japan and is probably distributed throughout the world. More recent investigations indicate that the infection is much commoner than these figures would suggest.

The virus can be demonstrated by the inoculation of susceptible animals. Mice and guinea pigs are most suitable, although monkeys are also susceptible. Mild or symptomless infections can be produced in several other species, including dogs. If cerebrospinal fluid or other infectious material is injected intracerebrally into mice, after an incubation period of about six days the mice become acutely ill, are prostrated and display clonic generalized convulsions with spasticity and hyperextension of the hind legs. Most of the mice die within a day or two. They show an intense infiltration of lymphocytes in the meninges and choroid plexus, but there are only minimal changes in the brain substance. They often also show interstitial pneumonia,

1. RIVERS, T. M., and SCOTT, T. F. M.: Meningitis in man caused by a filtrable virus, Science, 1935, lxxxi, 439.

2 TRAUB, E.: A filtrable virus recovered from white mice, Science, 1935, lxxxi, 439.

3 ARMSTRONG, C. R.: Studies on choriomeningitis and poliomyelitis, Harvey Lectures, 1940–41, 39–56.

4 FARMER, T. W., and JANEWAY, C. A.: Infections with the virus of lymphocytic choriomeningitis, Medicine, 1942, xxi, 1–63.

pleural effusions, and focal necroses in the liver, changes which indicate the generalized nature of the infection. The virus is present in these organs and in the blood. Similar lesions have been described in man in a few cases corresponding clinically to lymphocytic choriomeningitis, but there has as yet been no autopsy reported on a human case in which the virus was positively identified.

Those mice which survive recover completely, become free of virus and are specifically immune to reinfection. Mice also become immune following subcutaneous or intraperitoneal inoculation, although the infection so produced is usually mild or symptomless. Resistance to reinfection develops within a few days, although in this species no neutralizing antibodies have been demonstrated in the blood. This specific immunity makes possible the positive identification of a newly isolated strain of virus, by demonstrating that the latter causes typical symptoms in normal mice, but causes no infection in mice which have been immunized with a known strain of lymphocytic choriomeningitis virus.

There is much evidence that mice constitute the natural reservoir of the virus and that infection in man is acquired by contact with the secretions or excreta of such infected animals. Traub [2, 5] has reported an extensive study of the disease as it developed spontaneously in a colony of white mice. The infected mice transmitted the virus to their young in utero. Young mice often showed symptoms of illness but usually made a clinical recovery. Older mice rarely showed any evidences of infection. The virus, however, continued to be present in the blood, brain and other organs and was excreted in the nasal secretions, urine and feces throughout life. Under these conditions the mice appeared to develop a tolerance for the virus rather than an immunity, since traumatization of the brain, for example by intracerebral inoculation of sterile broth, will precipitate a severe and often fatal attack of encephalitis.

Gray house mice are also susceptible. They may carry the virus in their blood and tissues for months without manifest illness, they may convey it to the young in utero [4] and they excrete it in the urine and feces. Many naturally infected mice have been trapped. Armstrong and his associates [3] have shown that there is a close association between the natural infection in house mice and cases of human infection. They reported capturing infected mice in the homes of five out of six cases of lymphocytic choriomeningitis. Farmer and Janeway [4] have reported similar observations.

Guinea pigs can be infected about equally well by subcutaneous, intraperitoneal or intracerebral inoculation. After two to four days they show evident malaise, anorexia, emaciation, prostration and respiratory distress. Many die during the second week and show extensive visceral lesions, particularly interstitial pneumonia, as well as lymphocytic infiltration of the meninges. The virus is present in the blood and tissues generally. Ani-

[5] TRAUB, E.: Epidemiology of lymphocytic choriomeningitis in a mouse stock observed for four years, Jr. Exper. Med., 1939, lxix, 801.

mals which recover quickly develop resistance to reinfection and after a longer interval show virus-neutralizing antibodies in their blood.

Man is also susceptible to inoculation. Lépine et al.[6] gave subcutaneous inoculations of infected mouse brain emulsion to a series of volunteers. After an incubation period of two to three days fever developed, usually accompanied by prostration, malaise and general aching, clinically resembling "grippe." Virus was demonstrable in the blood. The fever usually lasted two to three weeks, but was often interrupted by one or two remissions. In about half the cases meningitis then developed, and the virus could be isolated from the cerebrospinal fluid. The others recovered without showing evidence of central nervous system involvement. In both groups neutralizing antibodies later appeared in the blood. The experimental infection in man, therefore, often runs its course without manifestations of meningeal involvement.

Epidemiological observations and immunological studies early led to the belief that this is also true of spontaneous human infections. Patients who recover from the disease, after two to three months, show specific neutralizing antibodies in their serum which may persist for several years. The presence of such protective power is regarded as proof of recovery from the infection.

In 1935 Armstrong and Wooly noted neutralizing power in the serum of an attendant who cared for infected animals, although he gave no history of meningitis, and they regarded this as probably the result of a systemic infection. Traub also reported the development under observation of antibodies in an attendant similarly engaged, who showed no clinical evidence of meningitis.

Since then Armstrong and his associates [3] have reported studies of 1000 sera from individuals without a history of any disease of the central nervous system, of which 10 per cent showed definite neutralizing power. Yamarat (quoted by Farmer and Janeway [4]) found 12 per cent positive among 126 miscellaneous patients in Boston. Armstrong also reported 26 per cent positive among 106 cases selected because of a history of recent upper respiratory tract infection. Direct proof of the occurrence of such spontaneous abortive cases was first brought by Armstrong and Hornibrook.[7] This was in a laboratory worker who had an acute illness with fever of a week's duration, malaise, backache, prostration and leukopenia, but showed no sign of meningitis. Virus was obtained from the blood. Before the illness the blood had shown no protective power, but six weeks later it was highly active.

These observations indicate that the infection is much more common than has been supposed, and that a large proportion of the cases are not recognized because they are virtually symptomless or present the indistinctive

[6] Lépine, P., Mollaret, P., and Kreis, B.: Receptivité de l'homme au virus murin de la chorioméningite lymphocytaire; reproduction expérimentale de la méningite lymphocytaire bénigne, Compt. rend. Acad. d. sci., 1937, cciv, 1846.

[7] Armstrong, C. R., and Hornibrook, J. W.: Choriomeningitis virus infection without central nervous system manifestations; report of a case, Pub. Health Rep., 1941, lvi, 907.

features of an ordinary "grippal" or upper respiratory infection. The older conception of the clinical features of the disease must be changed. After an incubation period of five to 10 days following exposure the disease starts abruptly with manifestations of a generalized systemic infection. There is fever, often undulant in type, prostration, anorexia, malaise and aching of a grippal type. Occasionally there are symptoms of an upper respiratory infection. The virus can be demonstrated in the blood which shows a leukopenia and granulocytopenia. In many cases, probably in a large majority, the fever subsides after from one to three weeks and the patient recovers completely.

In other cases, often after a brief remission, there is an abrupt recurrence of fever with severe general headache, backache, nausea, vomiting, and often some degree of drowsiness or mental disturbance. There are signs of meningeal irritation: a stiff neck, often photophobia, a positive Kernig sign and localized reflex disturbances, occasionally papilledema. The leukocyte count is normal or moderately elevated, the sedimentation rate is usually normal. The virus usually disappears from the blood at this time, but it can be obtained from the cerebrospinal fluid. The latter is clear or slightly opalescent, the pressure is often elevated, the protein content increased, and the cell count is increased, usually from 60 to 3000 per cu. mm., of which nearly all are lymphocytes. The fluid is usually normal in all other respects. After from one to four weeks as a rule the patient recovers completely. There may be considerable loss of weight and weakness and convalescence may be protracted.

In rare instances, as in two cases reported by Findlay et al.,[8] there may be an encephalitis. These cases show more profound mental disturbances, paralyses, gross reflex disturbances, and paresthesias or anesthesias. Recovery appears to follow as a rule, but there may be permanent sequelae. A few cases probably of this nature have come to autopsy, but the identity of the virus was not definitely established. The disease is not invariably benign.

The diagnosis can be established only by isolation and identification of the virus, or by demonstrating protective power (or other evidence of immune bodies) in the serum after recovery. Both are cumbersome procedures, possible only in well equipped laboratories. It is obvious that the diagnosis is rarely made or even suspected in cases showing only a systemic infection. Smadel,[9] however, has perfected a complement fixation technic which should be very useful for such work if its reliability is confirmed. A systematic study of cases of "influenza" and "atypical" pneumonia as well as aseptic meningitis would be desirable to determine the frequence and practical importance of the disease.

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REVIEWS

Chinese Lessons to Western Medicine. A Contribution to Geographical Medicine from the Clinics of Peiping Union Medical College. By I. SNAPPER, M.D.; foreword by GEORGE R. MINOT, Professor of Medicine, Harvard University. 380 pages; 16 × 24.5 cm. Interscience Publishers Inc., New York. 1941. Price, $5.50.

The occidental clinician will find in this brief volume an excellent introduction to the many special problems encountered in the practice of clinical medicine in North China. From the wards of the Peiping Union Medical College Hospital, Dr. Snapper has chosen material covering the entire range of internal medicine. Of chief interest to the Western clinician is the demonstration of geographical influence upon disease. The social and economic environment peculiar to this region likewise are shown to have their influence upon the manifestations of disease. Nutritional problems pervade every clinical picture and are ably discussed here. Numerous case abstracts are presented throughout the volume. All modern technics of study are fully utilized. Numerous original illustrations increase the value of the clinical presentations. Of particular interest are the sections devoted to such parasitic diseases as Kala-Azar and Schistosomiasis. Dr. Snapper has approached these subjects with an exceptionally broad background of clinical teaching and investigation. The material is presented in a manner calculated to hold the attention of the most discriminating reader.

M. S. S.

Brucellosis (Undulant Fever); Clinical and Subclinical. By HAROLD J. HARRIS, M.D. 305 pages; 24 × 16 cm. Paul B. Hoeber, Inc., N. Y. 1941. Price, $5.50.

This book is a concise practical treatise on brucellosis written by a practitioner and health officer especially for those whose interest lies in the management of this disease. The author has turned to the knowledge and experience gained through his personal contact with the disease to corroborate or refute the conclusions arrived at through a careful review of the literature.

Aside from a well-organized presentation and critical evaluation of diagnostic procedures and therapy, he has included chapters on the pathology, public health aspects as well as the medico-legal side of this disease.

This monograph evidences a thorough knowledge of the subject presented and a careful evaluation of the many difficulties encountered in diagnosis and treatment. The results of his personal experiences should prove of great value. Carefully planned, delightfully written, well-illustrated and attractively bound, it should prove a welcome addition to the working library of every physician.

J. A. W.

Diseases of the Nails. By V. PARDO-CASTELLO, M.D.; foreword by HOWARD FOX, M.D. 2nd Ed. 193 pages; 14.5 × 23.5 cm. Charles C. Thomas, Springfield, Ill. 1941. Price, $3.50.

Pardo-Castello's new textbook on Diseases of the Nails is a second edition of this useful monograph. Most of the 94 photographs are excellent and so supplement the text that the average reader can clearly grasp the pathologic changes which are described. The paper is excellent and the large clear type is very readable. The frequent use of the abused term, eczema, again demonstrates the need of an authori-

tative committee to define eczema or replace it by some acceptable term. The unscientific term ringworm is used too frequently in this technical text. The author has omitted some acceptable facts, such as the rapid and favorable response of granuloma pyogenicum to roentgen therapy. The second edition of this monograph brings up to date the only English symposium on diseases of the nails and should serve as an excellent reference for the physician and student interested in this subject.

F. A. E.

COLLEGE NEWS NOTES

The St. Paul Session of the College

The 26th Annual Session of the American College of Physicians, held in St. Paul, Minn., April 20–24, 1924, excelled all reasonable expectations. Although the gross attendance was smaller than during the last four or five years, it was nevertheless gratifying when one considers the location of the meeting city with respect to the center of population and the attendant war conditions. There were in attendance 1368 physicians, 75 medical students, 243 non-physician guests and 162 visiting wives or daughters of attending members; total 1848. The gross attendance from the leading states was as follows:

Minnesota	652	Michigan	66
Illinois	124	Wisconsin	66
Pennsylvania	101	Ohio	60
New York	99	California	45

The only states not represented were Idaho and Nevada. From Canada 25 were in attendance. Puerto Rico, Mexico and Argentina were represented.

Physical accommodations for the General Sessions, Panel Discussions, Clinics and Technical Exhibits were excellent, and everyone in attendance was able to obtain admittance to any program in which he was interested.

The entire program was marked by its outstanding excellence, and very few speakers were absent because of the war, although more than 12 per cent of the College membership is now on active military duty.

At the Convocation on Wednesday evening, April 22, 302 physicians were inducted to Fellowship, coming from 41 different states, the Medical Corps of the U. S. Army, the Medical Corps of the U. S. Navy, the U. S. Public Health Service, 2 provinces of Canada, from Panama and China.

The Ramsey County (Minn.) Medical Society, as host to the College, presented an excellent program of entertainment on Tuesday evening, April 21. It is regretted that the attendance at this particular function was small owing to the fact that the Annual Session program was so full that many members of the College overlooked this special feature.

The local Ladies' Entertainment Committee, with characteristic St. Paul hospitality and graciousness, entertained the 162 visiting women at numerous special functions.

The Annual Banquet, though not largely attended this year, was a festive occasion, and the guests were entertained by addresses by the President, the President-Elect and the speaker of the evening, Dr. William A. O'Brien, Director of Postgraduate Medical Education at the University of Minnesota, who gave many interesting and entertaining stories connected with "Medicine and the Public."

The Exposition and Technical Exhibit, though somewhat reduced in scope due to the high standards set by the College, was on a high, scientific and educational scale, and again merited the respect and the applause of all visiting physicians.

Dr. Roger I. Lee, of Boston, retired as President; Dr. James E. Paullin, of Atlanta, President-Elect, was inducted to office as President; Dr. Ernest E. Irons, of Chicago, was named President-Elect for the coming year. Dr. Charles H. Cocke, of Asheville, for many years Chairman of the Board of Governors of the College, was elected First Vice President. In appreciation and lasting recognition of Dr. Cocke's long and faithful service as Chairman of the Board of Governors, the Board unanimously voted that a silver ferruled gavel, engraved appropriately, be prepared and presented to Dr. Cocke. Dr. Henry R. Carstens, of Detroit, for many years

JAMES E. PAULLIN

PRESIDENT, AMERICAN COLLEGE OF PHYSICIANS, 1942–43

College Governor for Michigan, was elected Second Vice President; and Dr. A. C. Griffith, of Kansas City, for many years College Governor for Missouri, was elected Third Vice President. Dr. William B. Breed, Boston, was unanimously elected Chairman of the Board of Governors and thereby becomes ex officio a member of the Board of Regents. Dr. Chauncey W. Dowden, Louisville, continues as the Vice-Chairman of the Board of Governors.

Dr. Francis G. Blake, New Haven, Dr. Reginald Fitz, Boston, and Dr. Charles T. Stone, Galveston, were reëlected for a term of three years on the Board of Regents. Also elected to the Board of Regents was the retiring President, Dr. Roger I. Lee, of Boston, and Dr. James F. Churchill, of San Diego.

Dr. Robert O. Brown, Santa Fe, was elected Governor for New Mexico, succeeding the late Dr. LeRoy Peters. Among other new elections to the Board of Governors were Dr. Gilbert M. Stevenson, Ancon, Governor for Panama and the Canal Zone; Dr. Benjamin F. Wolverton, Cedar Rapids, Governor for Iowa; Dr. Edgar Hull, New Orleans, Governor for Louisiana; Dr. Douglas Donald, Detroit, Governor for Michigan; Dr. Ralph Kinsella, St. Louis, Governer for Missouri; Dr. Harry T. French, Hanover, Governor for New Hampshire; and Dr. Paul F. Whitaker, Kinston, Governor for North Carolina.

The personnel of new committees will be published in a succeeding issue of this journal, as will also the Minutes of the Board of Regents and of the Board of Governors.

James E. Paullin, M.D.

James E. Paullin, M.D., President-Elect, 1941–42, and President, 1942–43, American College of Physicians; born, Fort Gaines, Ga., November 3, 1881; A.B., Mercer University, 1900, continuing as graduate student through 1901; LL.D. (honorary), Mercer University, 1929; M.D., Johns Hopkins University School of Medicine, 1905; Resident Pathologist, Rhode Island Hospital, Providence, 1905–06; Resident, Piedmont Hospital, 1906–07; Pathologist, Georgia State Board of Health, 1907–11; Associate Professor of Pathology, Atlanta College of Physicians and Surgeons, 1907–11; Associate Visiting Physician, Grady Hospital, 1909–13; Visiting Physician and Chief of the Emory University Division, Grady Hospital, Atlanta; Professor of Clinical Medicine, Emory University School of Medicine since 1915. Major, Medical Corps, U. S. Army, 1918–19, serving as Chief of Medical Service, Camp Shelby, Miss. Former President (1913), Fulton County (Ga.) Medical Society; formerly President, Medical Association of Georgia; Member and former Chairman of the Medical Section, Southern Medical Association; Chairman of the Medical Section (1927), Chairman of the Council on Scientific Assembly (1939) and at present Member of the Medical Preparedness Committee, American Medical Association; former President (1937), American Clinical and Climatological Society; Member of the Association of American Physicians; Fellow of the American College of Physicians since 1928, serving for several years as Regent and Chairman of various Committees; Member of the Procurement and Assignment Agency, Office of Defense Health and Welfare, Federal Security Administration; Member of Sigma Nu, Phi Chi and Alpha Omega Alpha fraternities; Presbyterian; Member of the Capital City and Piedmont Driving Clubs; author of many papers published in the Journal of the Medical Association of Georgia, Southern Medical Association Journal, Journal of the American Medical Association, Annals of Internal Medicine, etc.; guest Professor of Medicine for one week at the Peter Bent Brigham Hospital in 1936 and Physician-in-Chief pro tempore at the Pratt Diagnostic Clinic of Tufts College Medical School, Boston.

ERNEST E. IRONS

PRESIDENT-ELECT, AMERICAN COLLEGE OF PHYSICIANS, 1942–43

Ernest E. Irons, M.D.

Ernest E. Irons, M.D., 122 S. Michigan Ave., Chicago, Ill. Born, Council Bluffs, Iowa, 1877; S.B., University of Chicago, 1900; M.D., Rush Medical College, Chicago, 1903; Ph.D., University of Chicago, 1912; Postgraduate work at the University of Vienna, 1909–10; Fellow in Bacteriology, University of Chicago, 1900–01; Assistant in Bacteriology, same, 1901–03; Internship at Presbyterian Hospital, Chicago; Assistant to Dr. James B. Herrick, widely known and revered Internist and Cardiologist of Chicago, 1905–12; served during World War I as Lieutenant Colonel in the Medical Corps of the U. S. Army; Member of the Council on Pharmacy and Chemistry of the American Medical Association, 1923–40; Dean, Rush Medical College, Chicago, 1923–36; Charter Member of the American Board of Internal Medicine since 1936, and Chairman of same since 1940; Rush Professor of Medicine, University of Illinois Medical School; Attending Physician, Presbyterian Hospital; Fellow of the American College of Physicians since 1929, and a member of its Board of Regents active on its various Committees since 1938; Member of the Chicago Medical Society, Illinois State Medical Society, Association of American Physicians, American Society for Clinical Investigation, Central Society for Clinical Investigation, Chicago Pathological Society, American Association of Pathologists and Bacteriologists, American Association for Study of Rheumatic Diseases, and others; author of many published papers.

The 1942 Annual Business Meeting

The General Business Meeting of the American College of Physicians convened at St. Paul, Minn., Thursday, April 23, 1942, with President Roger I. Lee presiding and Mr. E. R. Loveland acting as Secretary. The Secretary read abstracted minutes of the preceding Annual Business Meeting, which were approved as read.

The Treasurer, Dr. William D. Stroud, presented the following report:

"The finances of the American College of Physicians are under the general supervision of its Board of Regents and more specifically supervised by the Committee on Finance. The accounts are recorded in the Executive Offices according to accepted accounting principles and audited by a Certified Public Accountant.

"1941 operations indicate a satisfactory financial situation. The Endowment Fund on December 31, 1941, amounted to $132,586.38, the General Fund to $166,323.61, making the total College assets at book value $298,909.99. The net increase in capital for both Funds was $25,641.29. Full detailed financial statements will be published in an early issue of the Annals of Internal Medicine for the information of all members.

"On the recommendation of the Finance Committee and the subsequent approval of the Board of Regents, the budget for 1941 has been adopted, calling for an estimated income of $111,700.00 and estimated expenditures of $87,276.50. Respectfully submitted by William D. Stroud, Treasurer."

Mr. E. R. Loveland, as Executive Secretary, presented the following report:

"The Executive Secretary's report is supplementary to the reports of the Treasurer and Secretary General. Much that has happened in the College has also been referred to in the address of your President.

"The past year again has been characterized by an extension of activities of the College and in the duties of the Executive Offices, but at the same time our work has been rendered more interesting by its diversity. We have had at all times the cooperation and kindly aid of all the Officers, Regents and Governors. I should like especially to pay tribute to the members of the various College Committees that have

made such a contribution during the past year. Members at large have little opportunity to know how much time and effort these men devote to our organization.

"During the past year the volume basis of the "Annals of Internal Medicine" has been changed so that instead of one volume of twelve issues per year, we are publishing, for the sake of convenience of indexing and filing, two volumes each of six issues. A completely new and revised Directory of the College was published last Autumn and distributed to all members. Earlier in 1941, 1800 copies of the College History were reprinted so that there will be an adequate supply to furnish a copy to every new member entering the College. There have been numerous Regional Meetings conducted by College Governors for their particular states or regions, as a result of which there has been an increased participation by our members in College affairs. These meetings contribute greatly to a better understanding of the objectives and activities of your organization, and they will be of even greater importance in extending and cementing together the interests of our members in these times when attendance at the Annual Sessions may become more difficult.

"The work of preparing for this meeting has been lightened by the ready assistance and coöperation of President Lee, General Chairman Lepak and his efficient local committees. The registration totals 1848, of whom 162 are visiting women. Although these are not all members of the College, the great majority are.

"We know of no other national medical society that actually has as large a percentage of its members in attendance at its annual meetings as this College.

"We are always happy to welcome our members at the College Headquarters in Philadelphia. It is our desire to be of service to each one of you whenever and in whatever way it is possible. By all means, in these times, give your complete support and interest to our American Institutions, and especially I speak for the College. Our American Countries and England are the last outposts of such institutions as this College. In Continental Europe, all such organizations have been buried with their martyrs, and it behooves us to proceed with ever increasing zeal to preserve these societies through this war, else there will be no chance to return to the so-called 'American way of life' when this war is over."

The Secretary General, Dr. George Morris Piersol, presented the following report:

"*Membership*—Since the last Annual Session of the College we have lost by death 48 Fellows, 5 Associates, or a total of 53; by resignation, 3 Fellows, 11 Associates, total 14; by failure to qualify for advancement to Fellowship within the maximum five-year period prescribed by the By-Laws, 17 Associates; by delinquency, 7 Fellows and 2 Associates, total 9. The total membership mortality for the past year has been 93. There have been elected to Fellowship 302 physicians, only a few of whom were elected directly to Fellowship because of special qualifications and outstanding accomplishments. There have been elected to Associateship 220; 1 Fellow has been reinstated and 1 Fellow dropped from the roster because his whereabouts no longer can be determined. The total membership of the College as constituted is as follows:

4	Masters
3,728	Fellows
1,106	Associates
4,838	TOTAL

"*Life Membership*—16 Fellows have become Life Members during the past year, making a grand total of 183, of whom 17 are deceased, leaving 166 on the roll at this time.

"The Advisory Committee on Postgraduate Courses, with the whole-hearted cooperation of our officers, Regents and Governors, and many of our Fellows, has

conducted a series of Postgraduate Courses, some during February and some as premeeting courses. Eleven such courses were scheduled, but owing to conditions of war and other influences, 5 of these courses were cancelled, but the others were highly successful and well attended with a registration equivalent to that of the preceding year, even though some of our current courses were withdrawn. The College will continue this important work, and the schedule of courses for 1942–43 will be initially announced in the near future. The Advisory Committee on Postgraduate Courses during the past year has also initiated series of Postgraduate Lectures known as 'Postgraduate Nights,' for Medical Officers at one of the large naval hospitals in the East, and it is anticipated that this program will be extended to the larger base hospitals and naval hospitals in other parts of the country.

"Three additional research Fellowships have been awarded by the College to begin this coming summer or autumn."

Dr. Piersol, turning to President Lee and presenting him with an engraved, silver ferruled gavel, said:

"Mr. President, during the past year while you have so ably and wisely guided the destinies of this College you have become more than ever endeared to all who have had the privilege of working with you. We are deeply appreciative of the never-failing spirit of coöperation and courtesy that has marked all our association. Therefore, on behalf of the Officers, Regents and Governors of the American College of Physicians, I have the honor to present you with this Gavel, an enduring symbol of the high office you have held, as well as a token of our affection and esteem."

President Lee: "Thank you, Mr. Secretary General. It is with peculiar pleasure that I use this gavel for the first time in inducting the President-Elect, Dr. James E. Paullin, into the office of President."

Dr. Paullin, assuming the chair: "Dr. Lee, members of the College, ladies and gentlemen: To say that I am not deeply sensitive and appreciative beyond a mere expression of words of the honor which you have conferred upon me by elevating me to this, the highest office to be given by this Association, is but a feeble method of telling you the emotion that I feel at this time.

"When you made me President-Elect of this organization one year ago, the country was not facing the situation it now does. Things have changed, but with it there has been the growing interest and devotion of the members of the College to the purpose of National Defense.

"I again pledge my allegiance to the College and its membership, to do the best that I possibly can for the furtherance of that one objective which is foremost in the minds and hearts of every true, loyal American—the winning of this war and the preservation of the democratic thoughts and democratic ideals and the very things for which your forefathers and mine fought, bled and died. That now, is our job. Whatever it takes to accomplish that, you are willing, I am willing, all of us are willing to do.

"To that end I now pledge myself to you and you to me, so that it is unanimous."

President Paullin called for the report of the Committee on Nominations. Dr. Edward L. Bortz, Chairman of the Committee, presented the names of nominees for the elective offices, the Board of Regents and the Board of Governors. President Paullin acted upon each group individually and asked for nominations from the floor in accordance with provisions of the By-Laws. There were no nominations from the floor. Nominations for the various offices, by resolution regularly adopted, were closed and the nominees were elected by acclamation. (The names of the individuals so elected are published elsewhere in this issue of the ANNALS.)

President Paullin requested Colonel Hugh Morgan and Dr. Gorham Brigham to escort the President-Elect, Dr. Ernest E. Irons, to the rostrum. This was done amid applause from the audience.

DR. IRONS: "I am deeply appreciative of this signal honor, and especially so when I read the list of my distinguished predecessors. And as Dr. Paullin has noted, we are in the midst of a war—a war that we must win and shall win.

"In addition to pledging you my present efforts for the College, I also pledge that I shall do everything in my power to assist in the winning of this war. Thank you."

On motion by Dr. Thomas T. Holt, seconded by many, and carried by a unanimous rising vote, the following resolutions were adopted:

"BE IT RESOLVED, that the cordial and sincere thanks of the entire membership of the American College of Physicians be extended to our retiring President, Dr. Roger I. Lee, to the General Chairman, Dr. John Lepak, to the new President, Dr. James E. Paullin, to the chairmen and members of the St. Paul committees, individually and collectively, to Mrs. Edward Goltz and her efficient Committee on Ladies' Entertainment, for their faithful and courteous work in the conduct of this memorable Session; and

"BE IT FURTHER RESOLVED, that our appreciation be extended also to those cooperating agencies and the University of Minnesota Medical School, the hospitals, the public press, the Ramsey County Medical Society, Mr. Julius Perlt and the St. Paul Association of Commerce, and the management and staff of the Hotel Lowry and the Hotel St. Paul for their coöperation and help, all of which has contributed so much to our entertainment, pleasure and comfort."

There being no further business the meeting adjourned.

E. R. LOVELAND,
Executive Secretary

NEW ELECTIONS OF OFFICERS, REGENTS AND GOVERNORS

At the Annual Business Meeting of the American College of Physicians, Thursday, April 23, 1942, in St. Paul, Minn., the following were elected:

Officers

President-Elect ..... Ernest E. Irons, Chicago, Ill.
First Vice-President ..... Charles H. Cocke, Asheville, N. C.
Second Vice-President ..... Henry R. Carstens, Detroit, Mich.
Third Vice-President ..... A. Comingo Griffith, Kansas City, Mo.

Regents

Term Expiring 1945

Francis G. Blake, New Haven, Conn.
James F. Churchill, San Diego, Calif.
Reginald Fitz, Boston, Mass.
Roger I. Lee, Boston, Mass.
Charles T. Stone, Galveston, Tex.

Governors

Term Expiring 1943

Robert O. Brown, Santa Fe ..... NEW MEXICO

Term Expiring 1944

Gilbert M. Stevenson, Ancon ..... REPUBLIC OF PANAMA and the CANAL ZONE

Term Expiring 1945

Oliver C. Melson, Little Rock ..... ARKANSAS
Ernest H. Falconer, San Francisco ..... CALIFORNIA (Northern)
Benjamin F. Wolverton, Cedar Rapids ..... IOWA
Edgar Hull, New Orleans ..... LOUISIANA
Douglas Donald, Detroit ..... MICHIGAN
Edgar V. Allen, Rochester ..... MINNESOTA
Ralph Kinsella, St. Louis ..... MISSOURI
Lawrence Parsons, Reno ..... NEVADA
Harry T. French, Hanover ..... NEW HAMPSHIRE
George H. Lathrope, Newark ..... NEW JERSEY
Paul F. Whitaker, Kinston ..... NORTH CAROLINA
Julius O. Arnson, Bismarck ..... NORTH DAKOTA
Alexander M. Burgess, Providence ..... RHODE ISLAND
Kenneth M. Lynch, Charleston ..... SOUTH CAROLINA
Paul K. French, Burlington ..... VERMONT
Walter B. Martin, Norfolk ..... VIRGINIA
Charles E. Watts, Seattle ..... WASHINGTON
Albert H. Hoge, Bluefield ..... WEST VIRGINIA
Hugh A. Farris, St. John ..... MARITIME PROVINCES
Charles F. Moffatt, Montreal ..... QUEBEC

At a meeting of the Board of Governors, Wednesday, April 22, 1942, Dr. William B. Breed, Boston, Mass., was elected Chairman of the Board of Governors of the College. Dr. C. W. Dowden, Louisville, Ky., is Vice Chairman.

ELECTIONS TO MEMBERSHIP, ST. PAUL, APRIL 19, 1942

Elections to Fellowship

Ralph Irving Alford, Montclair, N. J.

Walter Hilmar Baer, Manteno, Ill.
Samuel Perkins Bailey, Brooklyn, N. Y.
Lyle Andrew Baker, Hines, Ill.
James Ian Baltz, Detroit, Mich.
Wendell Hugh Bennett, Youngstown, Ohio
Clifford Albert Best, (MC), U. S. Army
Henry Grady Bevil, Beaumont, Tex.
Samuel Blinder, New York, N. Y.
Edmund Clyde Boots, Pittsburgh, Pa.
Charles Arthur Breck, Wallingford, Conn.
Maurice Bruger, New York, N. Y.
George Nelson Burger, Covington, Ky.

Joseph Bishop Cady, Lebanon, Pa.
Eugene Calvelli, Port Washington, N. Y.
George Daniel Capaccio, Seattle, Wash.
John William Cass, Jr., Brookline, Mass.
Franklin Chester Cassidy, Fort Bayard, N. M.
Edwin Gurney Clark, Baltimore, Md.
Paul Chester Clark, Syracuse, N. Y.

Hunt Cleveland, Anniston, Ala.
James W. Colella, Johnson City, N. Y.
Thomas Bartholomew Cunnane, Los Angeles, Calif.
John DePaul Currence, New York, N. Y.
Hayden Harrison Cutler, Houston, Tex.

Earl Alfred Daugherty, Philadelphia, Pa.
John Arthur Daugherty, Harrisburg, Pa.
Boni James DeLaureal, New Orleans, La.
Preston Vine Dilts, Pittsfield, Ill.
Samuel Donner, Hartford, Conn.
Ralph Lafayette Drake, Wichita, Kans.
Morris Lionel Drazin, Jackson Heights, L. I., N. Y.

Franklin Gessford Ebaugh, Denver, Colo.
Benjamin Madison Eis, Brooklyn, N. Y.
Stanley Howard Erlenback, Rochester, N. Y.
Clayton Bernard Ethridge, Washington, D. C.
George Francis Evans, Clarksburg, W. Va.
James Bryan Eyerly, Chicago, Ill.

Theodore Richard Failmezger, Madison, N. J.
Carlos Eugene Fallon, Newburgh, N. Y.
Orin Jocevious Farness, Tucson, Ariz.
Robert Hanna Felix, U.S.P.H.S., Baltimore, Md.
David Irving Fertig, Hartsdale, N. Y.
Edgar Minton Fetter, San Diego, Calif.
James William Finch, Hobart, Okla.
Marion Stevenson Fitchett, Norfolk, Va.
Maurice Patrick Foley, Los Angeles, Calif.
Silas Crume Fulmer, Little Rock, Ark.
Joseph John Furlong, Milwaukee, Wis.

Lawrence Bernard Gang, Huntington, W. Va.
Thomas Cresson Garrett, Philadelphia, Pa.
Edwin Wilder Gates, Niagara Falls, N. Y.
Fred A. J. Geier, Washington, D. C.
William Roland Gibson, Los Angeles, Calif.
Olin Burr Gober, Temple, Tex.
Benjamin Elmer Goodrich, Dearborn, Mich.
Murray Eugene Goodrich, Toledo, Ohio
Robert William Gordon, Denver, Colo.
Randolph Bryan Grinnan, Jr., Norfolk, Va.
Herman Petrus Gunnar, Chicago, Ill.

William Richard Hallaran, Cleveland, Ohio
George Clifford Hamilton, Binghamton, N. Y.
Paul Victor Hamilton, Cincinnati, Ohio
Maurice A. F. Hardgrove, Milwaukee, Wis.
Tinsley Randolph Harrison, Winston-Salem, N. C.
Reid Russell Heffner, New Rochelle, N. Y.
Leon Hughes Hetherington, Pittsburgh, Pa.
William Roy Hewitt, Tucson, Ariz.

Ford Kimmel Hick, Oak Park, Ill.
Donald Frederick Hill, Tucson, Ariz.
Horton Corwin Hinshaw, Rochester, Minn.
Ralph Howard Homan, El Paso, Tex.
John Harlan Hornbaker, Hagerstown, Md.
Ralph Charles Hoyt, Reading, Pa.
Emry G. Hyatt, Tulsa, Okla.

Harold Joseph Jeghers, Boston, Mass.
Joseph Francis Jenovese, Hartford, Conn.
Walter Steen Jensen, (MC), U. S. Army
William Michael Jermain, Milwaukee, Wis.
Edward Morgan Jones, Endicott, N. Y.
Robert Harold Jones, Fairmont, W. Va.
Leonard Francis Jourdonais, Evanston, Ill.

Louis Nelson Katz, Chicago, Ill.
Samuel Russel Kaufman, Wilkes-Barre, Pa.
Marion Reginald King, U.S.P.H.S., Springfield, Mo.
Otis Gardner King, Bluefield, W. Va.
Estelle Elizabeth Kleiber, New Brunswick, N. J.
Charles John Koerth, San Antonio, Tex.
Joseph Rudolph Kriz, Toledo, Ohio

Leo Frederick La Palm, Rochester, N. Y.
Albert Theodore Leatherbarrow, Hampton Station, N. B.
Edward Paul Leeper, Dallas, Tex.
Seaborn Joseph Lewis, Beaumont, Tex.
James J. Lightbody, Detroit, Mich.

Chauncey Carter Maher, Chicago, Ill.
Tim Joseph Manson, Chattanooga, Tenn.
Frank Baker Marsh, Salisbury, N. C.
Frederick Eugene Marsh, Chattanooga, Tenn.
Ernest George McEwen, Evanston, Ill.
Robert McGrath, New York, N. Y.
Floyd Thomas McIntire, San Angelo, Tex.
Frank Meyers, Buffalo, N. Y.
Fred Nathan Miller, Eugene, Ore.
Ralph Bretney Miller, Boston, Mass.
Lester M. Morrison, Philadelphia, Pa.
Emma Sadler Moss, New Orleans, La.
William Peter Mull, (MC), U. S. Navy
Wendell Stanley Muncie, Baltimore, Md.

John Noll, Jr., Youngstown, Ohio
Thomas Ochsner Nuzum, Janesville, Wis.

Arthur Martin Olsen, Rochester, Minn.

Henry Felch Page, Philadelphia, Pa.
Robert Clinton Page, Mount Vernon, N. Y.
Franklin Bruce Peck, Indianapolis, Ind.

George Peter Perakos, New Britain, Conn.
William Harvey Perkins, Philadelphia, Pa.
Elbert Lapsley Persons, Durham, N. C.
Aaron Robert Peskin, New York, N. Y.
Helen Sinclair Pittman, Boston, Mass.
Harry William Primakoff, Baltimore, Md.

Harold Lawrence Rakov, Kingston, N. Y.
Edward Conrad Reifenstein, Jr., Syracuse, N. Y.
Murray Lambert Rich, Covington, Ky.
Isidore Leon Robbins, New Orleans, La.
Donald Herbert Root, Quincy, Ill.
Abraham Rudy, Boston, Mass.
Nelson G. Russell, Jr., Buffalo, N. Y.

Oscar Adam Sander, Milwaukee, Wis.
John Albert Schindler, Monroe, Wis.
Curt Paul Schneider, Detroit, Mich.
Otis B. Schreuder, (MC), U. S. Army
John William Scott, Edmonton, Alta.
Grady Oscar Segrest, Mobile, Ala.
Joseph Haskell Shaffer, Detroit, Mich.
William Woolf Shapiro, Chicago, Ill.
John Charles Sharpe, Omaha, Nebr.
Joseph Dunbar Shields, Jr., Concord, N. H.
Donald Sanford Smith, Pontiac, Mich.
Opie Norris Smith, Greensboro, N. C.
William Andrew Somerville, New York, N. Y.
Clair Grove Spangler, Reading, Pa.
Wesley William Spink, Minneapolis, Minn.
Aaron Alfred Sprong, Sterling, Kan.
Harold Jones Starr, Chattanooga, Tenn.
Alfred Stengel, Jr., Philadelphia, Pa.
Ralph Eugene Swope, New York, N. Y.

Samuel Gale Taylor, III, Chicago, Ill.
Harry Burger Thomas, York, Pa.
Harry Edward Thompson, Tucson, Ariz.
Richard Carmichael Tilghman, Baltimore, Md.
Warren Irving Titus, Glen Cove, L. I., N. Y.

Howard Wakefield, Chicago, Ill.
Frank Bolles Wakeman, (MC), U. S. Army
Albert Wicken Wallace, Miami Beach, Fla.
Robert Pulley Wallace, New York, N. Y.
James Alexander Walsh, Peoria, Ill.
Albert Gayden Ward, Jackson, Miss.
Richard Nathaniel Washburn, Rensselaer, Ind.
Walter Weissenborn, Hartford, Conn.
Merritt Bryant Whitten, Dallas, Tex.
William Lewis Winters, Highland Park, Ill.
Francis Roman Wise, York, Pa.
Sidney Elmer Wolpaw, Cleveland, Ohio

Lawrence Foss Woolley, Towson, Md.

Frederick Otto Zillessen, Easton, Pa.

Elections to Associateship

Harold Herbert Aaron, New York, N. Y.
Carl Richard Ahroon, Jr., Bloomington, Ill.
Charles Henry Armentrout, Asheville, N. C.
Philip Klaus Arzt, Jamestown, N. D.

Gerald Seler Backenstoe, Emmaus, Pa.
Roland Wellington Banks, Yeadon, Pa.
Duncan William James Bell, Providence, R. I.
Maxwell Rufus Berry, Jr., Richmond, Va.
Earl Julius Bieri, Hot Springs National Park, Ark.
Samuel Blackwell, Memphis, Tenn.
William Cooper Buschemeyer, Louisville, Ky.
Benjamin Burroughs Bushong, Traverse City, Mich.

Donald Clarence Campbell, Rochester, Minn.
Eugene Charles Chamberlain, Fort Lauderdale, Fla.
Donald Tillinghast Chamberlin, Boston, Mass.
Herman Maurice Chesluk, Detroit, Mich.
William Godfrey Childress, Valhalla, N. Y.
Abraham George Cohen, New York, N. Y.
Samuel James Cohen, Brooklyn, N. Y.

James Stuart Daly, Trail, B. C.
William Hill Dearing, Rochester, Minn.
Rurico Santiago Diaz Rivera, San Juan, P. R.
William Clay Dine, Jr., Amarillo, Tex.
Henry Dolger, New York, N. Y.
Charles William Dowden, Louisville, Ky.
Harold Raymond Drysdale, Rochester, N. Y.

Samuel Lawrence Ellenberg, New York, N. Y.
Hugo Tristram Engelhardt, New Orleans, La.
John Paul English, Rochester, Minn.

James Brookbank Fisher, Wichita, Kan.
Ralph Gibson Fleming, Durham, N. C.
Harry Thomas Foley, II, Pittsburgh, Pa.
Roberto Francisco Azize, Arecibo, P. R.

William Robert Galbreath, Jr., New Orleans, La.
Russell Arthur Garman, Jeannette, Pa.
Samuel M. Gingold, Detroit, Mich.
Eddie Monroe Gordon, Jr., U.S.P.H.S., Mobile, Ala.
Richard Sigmund Gubner, Brooklyn, N. Y.

James Whitney Hall, Jr., Chicago, Ill.
William Marion Hall, Shreveport, La.
Ralph Orville Hayden, St. Charles, Mo.

George Anthony Hellmuth, Chicago, Ill.
Thomas Robert Hepler, Harrisburg, Pa.
Howard Eugene Heyer, Chicago, Ill.
Robert Emmett Hobbs, Shenandoah, Pa.
Harold Jennings Hoxie, Los Angeles, Calif.

William Knowlton Ishmael, Oklahoma City, Okla.

George Miller Jones, Ann Arbor, Mich.

Mennasch Kalkstein, New York, N. Y.
Solomon Salkind Kauvar, Denver, Colo.
Paul Edmund Keller, (MC), U. S. Army
Richard James Kilhullen, Wilkes-Barre, Pa.
Laurance Wilkie Kinsell, East Stroudsburg, Pa.
Jack D. Kirshbaum, Chicago, Ill.
Solomon Krell, New York, N. Y.
Maurice Alexander Kugel, Miami Beach, Fla.
Franklin Arthur Kyser, Galesburg, Ill.

Edwin Lever Lame, Philadelphia, Pa.
Clarence Watson LeDoux, Baltimore, Md.
Howard James Lee, Oshkosh, Wis.
Harry D. Leinoff, New York, N. Y.
Bernard Isaac Lidman, Norfolk, Va.
David Frank Loewen, Decatur, Ill.
Alexander Leon Louria, Brooklyn, N. Y.

William David Mackay, Mount Vernon, N. Y.
John Edward Manley, Scranton, Pa.
Donald Feige Marion, Detroit, Mich.
Ralf Martin, Portland, Maine
Robert Archibald Matthews, Philadelphia, Pa.
Milton John Matzner, Brooklyn, N. Y.
Thomas Crooke McCleave, Jr., Oakland, Calif.
George Gordon McHardy, New Orleans, La.
Christopher John McLoughlin, Rochester, Minn.
Robert Lindsay McMillan, Winston-Salem, N. C.
Ronald John McNamara, Charleston, W. Va.
Leo Joseph Meienberg, Portland, Ore.
Paul Reims Meyer, Port Arthur, Tex.
Raymond Everett Miller, New York, N. Y.
Lawrence T. Minish, Jr., Louisville, Ky.
William John Mitchell, Los Angeles, Calif.
Martin Alvin Murphy, Brooklyn, N. Y.

Edward Stewart Orgain, Durham, N. C.

James Earl Patterson, Buffalo, N. Y.
Horace Pettit, Philadelphia, Pa.
Harry Harvey Pote, Philadelphia, Pa.

Leland Paul Ralph, Grand Rapids, Mich.
Henry Rascoff, Brooklyn, N. Y.

Richard Reeser, Jr., Daytona Beach, Fla.
Max Harry Rosenblum, Steubenville, Ohio
Abraham Isaac Rosenstein, New York, N. Y.
Chauncey Lake Royster, Raleigh, N. C.
Henry Irving Russek, U.S.P.H.S., Brooklyn, N. Y.

Martin Schaeffer, Detroit, Mich.
Eugene Mathias Schloss, Philadelphia, Pa.
George Schwartz, New York, N. Y.
Lamont R. Schweiger, Shorewood, Wis.
Maurice McLaurin Scurry, Ann Arbor, Mich.
Louis Bernard Shapiro, Manteno, Ill.
Edward David Sherman, Sydney, N. S.
Seymour Harry Silvers, Brooklyn, N. Y.
Alfred Harvey Simmons, Harrisburg, Pa.
Howard Nellson Simpson, Springfield, Mass.
Ben Slutzky, Omaha, Nebr.
Kendrick Adelbert Smith, Rochester, Minn.
Lucian Anderson Smith, Rochester, Minn.
Wilbur Anderson Smith, New York, N. Y.
Charles Keith Stuart, London, Ont.
Stanley Richard Szymanski, Livingston, N. Y.

Henry Allen Tadgell, Boston, Mass.
William Garland Talmage, Succasunna, N. J.
Arthur Martin Tiber, New York, N. Y.
James Eugene Toups, New Orleans, La.

Frank Carl Val Dez, Chicago, Ill.
Aloysius Vass, Springfield, Ill.
Walter Lyle Voegtlin, Seattle, Wash.
Earl Stanley Vollmer, Glenside, Pa.

Leon Hugh Warren, Washington, D. C.
Alton Floyd Williams, Fort Jackson, S. C.
William Hays Windley, New Orleans, La.

Ellis William Young, Pittsburgh, Pa.

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows:

American Board of Internal Medicine:
William S. Middleton, M.D., Secretary
1301 University Ave.
Madison, Wis.

Written Examinations: October 19, 1942; applications for admission must be filed before September 1, 1942.

Oral Examinations: Philadelphia, Pa., June, 1942, in advance of the meeting of the American Medical Association in Atlantic City, N. J.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: C. Guy Lane, M.D., Secretary 416 Marlboro St. Boston, Mass.	*Written Examinations:* Will be given in various centers November 16, 1942; applications for admission must be filed before October 6, 1942. *Oral Examinations:* Cleveland, Ohio, January 14–15, 1943; applications for admission must be filed before December 8, 1942.
AMERICAN BOARD OF PEDIATRICS: C. A. Aldrich, M.D., Secretary 707 Fullerton Ave. Chicago, Ill.	*Written Examinations:* Locally September 18, 1942. *Oral Examinations:* Chicago, Ill., November 2–3, 1942, in advance of the meeting of the American Academy of Pediatrics; applications for admission must be filed before July 1, 1942.
AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N.W. Washington, D. C.	*Written Examinations:* New York, N. Y., December, 1942; applications for admission must be filed before October 1, 1942.
AMERICAN BOARD OF RADIOLOGY: B. R. Kirklin, M.D., Secretary Mayo Clinic Rochester, Minn.	*Oral Examinations:* Atlantic City, N. J., June 4–6, 1942; November, 1942 (date and place not yet selected).

For further details and application forms communicate with the respective secretaries.

REGIONAL MEETING OF FLORIDA MEMBERS

The Florida Chapter of the American College of Physicians held its Annual Regional Meeting in Hollywood, Florida, on April 13. The program was as follows:

1. "Clinical Management of Hodgkin's Disease."
   (*a*) Clinical Viewpoint:
   W. Wellington George, F.A.C.P., West Palm Beach.
   (*b*) Radiological Viewpoint:
   F. K. Herpel, F.A.C.P., West Palm Beach.
2. "X-Radiation in the Treatment of Pituitary Basophilism."
   George R. Crisler (Associate), Winter Park.
3. "Gastrointestinal Lesions Simulating Angina Pectoris."
   Paul B. Welch, F.A.C.P., Miami.
4. "Résumé on Nephrosis in Childhood."
   J. Sudler Hood (Associate), Clearwater.

The Chapter voted unanimously and the secretary was instructed to communicate with the College Governor for Georgia, recommending that the College be invited to hold its 1943 Annual Session in Atlanta, Georgia, the general feeling being that this would be a proper tribute to the incoming President, Dr. James E. Paullin, of Atlanta.

The Chapter also voted unanimously to recommend through its Governor, Dr. T. Z. Cason, that the Board of Regents consider holding the Annual Session of the College either at a later date in the spring or at an early date in the autumn. This action was recommended because of the difficulty Florida members experience in attending the Sessions since these convene at a time when doctors in territories dependent upon the tourist season are unable to leave their practices. When the College some years ago changed the date of its Annual Sessions from February to April, these physicians were helped considerably for some two years, but the tourist season in the south has changed, fluctuating from the later winter through early spring. The Florida Chapter felt that many southern states depend upon business from winter tourists and that many others, besides those from Florida, are handicapped by holding the Meeting in early April.

Gifts to the College Library

Acknowledgment is made of the receipt of the following reprints of publications by members of the College:

Dr. Benjamin R. Allison, F.A.C.P., Hewlett, N. Y.—1 reprint;
Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y.—4 reprints;
Dr. J. Edward Berk (Associate), Philadelphia, Pa.—2 reprints;
Dr. Leon L. Blum (Associate), Terre Haute, Ind.—1 reprint;
Dr. Eugene P. Campbell (Associate), Philadelphia, Pa.—11 reprints;
Dr. Lyman B. Carruthers, F.A.C.P., Miraj, S. M. C., India—2 reprints;
Dr. Darrell C. Crain, Jr. (Associate), Washington, D. C.—1 reprint;
Dr. Irving Greenfield (Associate), Brooklyn, N. Y.—2 reprints;
Dr. George F. Harsh (Associate), San Diego, Calif.—5 reprints;
Dr. Oswald F. Hedley, U.S.P.H.S., Bethesda, Md.—1 reprint;
Dr. Arthur A. Herold, F.A.C.P., Shreveport, La.—4 reprints;
Dr. Earl Jones, F.A.C.P., Alexandria, La.—1 reprint;
Oza J. LaBarge, F.A.C.P., Major (MRC), U. S. Army—1 reprint;
Dr. Evans W. Pernokis (Associate), Chicago, Ill.—1 reprint;
Dr. Max Pinner, F.A.C.P., New York, N. Y.—2 reprints;
Dr. Samuel G. Plice, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. William T. Rainey, F.A.C.P., Fayetteville, N. C.—1 reprint;
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Martin E. Rehfuss, F.A.C.P., Ardmore, Pa.—2 reprints;
Dr. Nathaniel E. Reich (Associate), Brooklyn, N. Y.—4 reprints;
Dr. Horace K. Richardson, F.A.C.P., Baltimore, Md.—1 reprint;
Dr. Rafael Rodriguez-Molina, F.A.C.P., San Juan, P. R.—1 reprint;
Dr. Albert H. Rowe, F.A.C.P., Oakland, Calif.—2 reprints;
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—2 reprints;
Dr. Jacob J. Singer, F.A.C.P., Los Angeles, Calif.—2 reprints;
Dr. Lester D. Watson (Associate), Milton, Mass.—2 reprints.

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Reuben Finkelstein, Brooklyn, N. Y.
Dr. Arthur A. Herold, Shreveport, La.

Under the Presidency of Dr. Herman O. Mosenthal, F.A.C.P., New York, N. Y., the American Diabetes Association will hold its 2nd Annual Meeting in Atlantic City, N. J., on June 7, 1942. The annual business meeting will be held during the morning and will be followed by the Presidential Address. After this address there will be a round table discussion with Dr. Mosenthal acting as Chairman, and Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, Pa., Dr. Edward S. Dillon, F.A.C.P., Philadelphia, Pa., and Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., participating. During the afternoon scientific session the following members of the College will present papers:

Dr. Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—"Action of Insulin";
Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, Pa.—"The Diabetic in the Defense Program";
Dr. Eaton M. MacKay, F.A.C.P., La Jolla, Calif.—"Acidosis."

Dr. Roger I. Lee, F.A.C.P., Boston, Mass., was recently made an honorary Fellow of the Royal College of Physicians of England.

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, Pa., addressed the Buffalo Academy of Medicine at Buffalo, N. Y., April 8, 1942, on "Pathology and Rational Therapy of Chronic Arthritis." On April 23, 1942, Dr. Pemberton delivered an address before the students of the Long Island College of Medicine, Brooklyn, N. Y.

Dr. Seeley G. Mudd, F.A.C.P., Pasadena, Calif., has been appointed Dean of the University of Southern California School of Medicine, Los Angeles.

Dr. Lester Neuman, F.A.C.P., Washington, D. C., addressed the New Castle County Medical Society in Wilmington, Del., January 20, 1942. Dr. Neuman spoke on "New Horizons in Clinical Pathology."

Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., was elected one of the Vice Presidents of the Delaware Public Health Association, at a recent meeting.

On March 20, 1942, Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., addressed the Northwest Branch of the Chicago Medical Society. The subject of Dr. Christie's address was "What Is Being Done to Control Cancer."

Among the speakers at the meeting of the Central Neuropsychiatric Hospital Association in Des Moines, Iowa, March 19–20, 1942, were:

Dr. George T. Harding, III, F.A.C.P., Columbus, Ohio—"Acute Problems Facing the Private Psychiatric Hospital";
Dr. Titus H. Harris, F.A.C.P., Galveston, Tex.—"Psychiatry and the National Emergency";
Dr. William C. Menninger, F.A.C.P., Topeka, Kan.—"Morale and the Private Psychiatric Hospital."

The Medical Society of the State of New York recently sponsored a postgraduate course on "Arteriosclerosis and Aging" for the Jefferson County (N. Y.) Medical Society. Among those who conducted the course were:

April 23, 1942, Dr. S. Bernard Wortis, F.A.C.P., New York, N. Y.—"Neuropsychiatric Aspects; Diagnosis and Treatment";

May 14, 1942, Dr. William Goldring, F.A.C.P., New York, N. Y.—"Renal and Cardiac Aspects; Diagnosis and Treatment";

May 21, 1942, Dr. Irving S. Wright, F.A.C.P., New York, N. Y.—"Peripheral Vascular Aspects; Diagnosis and Treatment."

On April 2, 1942, Dr. James S. McLester, F.A.C.P., Birmingham, Ala., Professor of Medicine, University of Alabama School of Medicine, delivered the Hermann M. Biggs Memorial Lecture at the New York Academy of Medicine. Dr. McLester spoke on "Nutrition and the Nation at War."

Dr. Frederick W. Williams (Associate), New York, N. Y., was one of the speakers at a symposium on "Reduction in Mortality Due to Gangrene in the Diabetic," at a recent clinical meeting of the New York Diabetes Association.

Dr. John G. Mateer, F.A.C.P., Detroit, Mich., spoke on "Comparative Sensitivity and Reliability of the Newer Liver Function Tests and Their Relationship to Medical and Surgical Problems" at a meeting of the Academy of Medicine, of Cincinnati, Ohio, February 17, 1942.

Dr. R. Lomax Wells, F.A.C.P., Washington, D. C., has been elected Chairman of the Interprofessional Conference, a new organization sponsored by the Medical Society of the District of Columbia to discuss the mutual problems of the pharmaceutic, dental and nursing professions.

The Midwestern Section of the American Congress of Physical Therapy held its spring session April 6, 1942, in Iowa City, Iowa. At this meeting Dr. Max K. Newman (Associate), Detroit, Mich., spoke on "Hypothermic Anesthesia in Extremity Surgery," and Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., spoke on "The Relation of Physical Therapy in War."

The Iowa State Medical Society held its 91st Annual Session in Des Moines, Iowa, April 15–17, 1942. Among the guest speakers were:

Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio—"Differential Diagnosis of Meningeal Irritations";

Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—"Certain Peculiarities of Gallstone Disease."

Dr. Edward B. Krumbhaar, F.A.C.P., Philadelphia, Pa., delivered a public lecture sponsored by the College of Physicians of Philadelphia, on "Superstition and Medical Progress."

The Mary Scott Newbold Lecture of the College of Physicians of Philadelphia was delivered on May 6, 1942, by Dr. C. Sidney Burwell, F.A.C.P., Boston, Mass. The subject of Dr. Burwell's lecture was "Studies of the Circulation in Congenital Affections of the Heart and Their Application to Some of the Problems of Heart Disease."

The Philadelphia County Medical Society held its 7th Annual Postgraduate Institute in Philadelphia, April 13–17, 1942. Among the local speakers at this Symposium on Modern Therapy were:

Dr. T. Grier Miller, F.A.C.P.—"The Significance of Nutrition in Relation to National Defense";

Dr. G. Harlan Wells, F.A.C.P.—"Diabetes Complicated by Tuberculosis";

Dr. Charles C. Wolferth, F.A.C.P.—"The Management of Coronary Disease in the Diabetic";

Dr. Harrison F. Flippin, F.A.C.P.—"Recent Advances in Sulfonamide Therapy";

Dr. William G. Leaman, Jr., F.A.C.P.—"The Management of the Cardiovascular Complications of Anemia and the Deficiency Diseases";

Dr. Ralph Pemberton, F.A.C.P.—"Effective Organization of the Treatment of Arthritis."

At the meeting of the Tri-State Medical Association of the Carolinas and Virginia in Greenville, N. C., February 23–24, 1942, Dr. George R. Wilkinson (Associate), Greenville, was installed as President and Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., was named a Vice President.

The American Association of Pathologists and Bacteriologists held its 42nd Annual Meeting in St. Louis, Mo., April 2–3, 1942. Among the speakers were:

Dr. Carl V. Weller, F.A.C.P., Ann Arbor, Mich.—"Statistical Investigation of the Correlation Between Mastopathia Cystica and Mammary Cancer";

Dr. Jacob Werne, F.A.C.P., Jamaica, N. Y.—"Postmortem Evidence of Acute Infection in Unexpected Death of Infancy and Childhood";

Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio—"General Considerations of Functioning Tumors of Endocrine Glands";

Dr. Ernest M. Hall, F.A.C.P., Los Angeles, Calif.—"The Incidence of Rheumatic Stigmas in Nonrheumatic Hearts."

Dr. Logan Clendening, F.A.C.P., Kansas City, Mo., spoke on "The Place of Obstetrics in the Various Epochs of the History of Mankind," and Dr. Alexander E. Brown, F.A.C.P., Rochester, Minn., spoke on "History and Pharmacologic Aspects of Chemotherapeutic Drugs," at the 2nd American Congress on Obstetrics and Gynecology held in St. Louis, Mo., April 6–10, 1942.

The American Society for Pharmacology and Experimental Therapeutics held its annual meeting in Boston, Mass., March 31–April 4, 1942. During a symposium on "Morphine Problems," Dr. Harold G. Wolff, F.A.C.P., New York, N. Y., spoke on "Pain and Its Relief by Morphine and Related Substances," and Dr. Clifton K. Himmelsbach (Associate), Lexington, Ky., spoke on "Present Status of Morphine Addiction Studies"; during a symposium on "Deficiency Diseases," Dr. Norman H. Jolliffe, F.A.C.P., New York, N. Y., presented a paper on "Vitamins in the Practice of Medicine," and Dr. William H. Sebrell, Jr., F.A.C.P., Washington, D. C., presented a paper on "Vitamins in Public Health."

The 69th Annual Meeting of the Florida Medical Association was held in Hollywood, Fla., April 13–15, 1942. Among the speakers were:

Dr. James A. Bradley, F.A.C.P., St. Petersburg, Fla.—"Bed Rest in Coronary Thrombosis";

Dr. Warren W. Quillian, F.A.C.P., Coral Gables, Fla.—"Pyurias in Childhood: Their Significance and Treatment."

Dr. William C. MacCarty, F.A.C.P., and Dr. Byrl R. Kirklin, F.A.C.P., both of Rochester, Minn., spoke on "Radiologic and Pathologic Studies of Prepyloric Ulcer," at the spring meeting of the Minnesota Radiological Society held in Rochester, March 28, 1942.

Among the speakers at the annual session of the Missouri State Medical Association held in Kansas City, Mo., April 27–29, 1942, were:

Dr. Karl W. Brimmer, F.A.C.P., Washington, D. C.—"Faith, Hope and Cure-Alls";

Dr. George R. Herrmann, F.A.C.P., Galveston, Tex.—"Some Medical Emergencies and Their Management";

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio—"The Differentiation of Obscure Anemia";

Dr. Irvine H. Page (Associate), Indianapolis, Ind.—"Hypertension and Its Experimental Treatment";

Dr. Raymond O. Muether (Associate), St. Louis, Mo.—"Blood Banks."

George F. Lull, F.A.C.P., Colonel (MC), U. S. Army, addressed the annual banquet meeting on "The Medical Officer in Our Wartime Army."

Recently Dr. George C. Owen (Associate), Oshkosh, Wis., was elected President and Dr. Einar R. Daniels (Associate), Milwaukee, Wis., Vice-President of the Wisconsin Trudeau Society.

Dr. Jeremiah Fletcher Lutz, F.A.C.P., and Dr. Francis R. Wise, F.A.C.P., both of York, Pa., have been appointed Chairman and Co-Chairman, respectively, of the Emergency Medical Service of York and York County.

Under the Presidency of Dr. Harry V. Paryżek, Cleveland, Ohio, the Ohio State Medical Association held its 96th Annual Session in Columbus, April 28–30, 1942. Among the guest speakers were:

Dr. Chester S. Keefer, F.A.C.P., Boston, Mass.—"Chemotherapy";

Dr. Richard H. Freyberg (Associate), Ann Arbor, Mich.—"Recent Trends in the Treatment of Rheumatoid Arthritis";

Leonard G. Rowntree, F.A.C.P., Colonel (MRC), U. S. Army—"Health and National Defense";

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn.—"Physical Therapy in General Practice."

Dr. Harold I. Gosline, F.A.C.P., has been appointed Medical Director of the Ring Sanatorium and Hospital of Arlington Heights, Mass.

Dr. Reginald C. Edson (Associate) recently resigned as Assistant Superintendent and Medical Director of the Hopemont State Tuberculosis Sanitarium and as Instructor in Medicine at the West Virginia University School of Medicine to accept the position of Assistant Director of Tuberculosis Control for the State of Connecticut. Dr. Edson is now located at 36 Westfield Road, West Hartford.

On January 1, 1942, Dr. John Levan (Associate), Reading, Pa., was made Chief of the Department of Cardiology of St. Joseph's Hospital.

Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, Pa., addressed the Dade County Medical Society at the Jackson Memorial Hospital on April 1, 1942, in Miami, Florida. His subject was "Diabetes Mellitus: The Most Scientifically Treated of All Diseases."

Dr. Louis Faugeres Bishop, Jr., F.A.C.P., after enlisting in the Army, has been commissioned in the Medical Corps as a Major in the Army Air Forces. He has been assigned to Kelly Field, San Antonio, Texas.

OBITUARIES

DR. HARRY CATTELL FISLER

Dr. Harry Cattell Fisler died in Jefferson Hospital on February 20, 1942. Dr. Fisler, who resided in Easton, Pa., had been an Associate of the American College of Physicians since 1924.

Dr. Fisler received his A.B. and A.M. degrees from Lafayette College, and his M.D. degree from the University of Pennsylvania School of Medicine in 1895.

In former years, Dr. Fisler served as Laryngologist at Easton Hospital, but since 1924 he devoted most of his time to pediatrics.

He was active in medical groups, having membership in the Lehigh Valley Medical Society, Northampton County Medical Society, Pennsylvania State Medical Society, and the American Medical Association.

Since he had a pleasing personality, Dr. Fisler was admired and liked by his professional colleagues and friends, and it is with a sense of loss that we write of his passing.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ALBERT E. AUSTIN

Dr. Albert Elmer Austin, Old Greenwich, Conn., Fellow of the American College of Physicians since 1925, died January 26, 1942, of carcinoma of the lung.

Dr. Austin was born in Medway, Mass., in 1877. He attended the public schools and later entered Amherst College, where he was a member of Phi Beta Kappa, obtaining both his A.B. and A.M. degrees in 1899.

After a short period of teaching, he entered Jefferson Medical College of Philadelphia, graduating in 1905. Dr. Austin began the practice of medicine in Medway, but soon came to Old Greenwich where he resided until his death.

In Greenwich Dr. Austin had a notable career. For many years he was the Director of Medical Service at both the Greenwich and the Municipal Hospitals, the latter established largely through his efforts.

Dr. Austin was Health Officer for twenty years, a member and Past President of the Greenwich Medical Society, member of his County, State and National Medical Societies, member of the Royal Society of Medicine in England, bank president, Representative in the State Legislature for two terms, U. S. Congressman from 1938 to 1940, and during the World War, Regimental Surgeon of the 214th Engineers, 14th Division, U. S. Army.

Dr. Austin was also a Thirty-third Degree Mason, well known and in great demand as an after-dinner speaker and orator on many occasions. At the time of his death he was Consulting Internist to the Greenwich Hospital.

His life, which was full and varied, was devoted to the service of others. His death has removed an able internist from the medical profession, and his many friends and acquaintances will feel the loss of this public-spirited citizen.

CHARLES H. TURKINGTON, M.D., F.A.C.P.,
Governor for Connecticut

DR. PHILIP FINKLE

Dr. Philip Finkle, of 1000 Park Avenue, New York City, died on March 12, 1942, from coronary thrombosis, at Miami Beach, Florida, where he moved last December expecting to practice medicine.

Dr. Finkle was born in Hartford, Connecticut, November 2, 1894. He received his A.B. degree from Columbia University in 1916 and his M.D. degree from the Columbia University College of Physicians and Surgeons in 1918. Dr. Finkle served his internship at the Mount Sinai Hospital, New York, between 1918 and 1920 and from 1920 to 1922 he was Admitting Physician to this Hospital. From 1922 to 1923 he undertook postgraduate work at the University of California; from 1923 to 1925 he did postgraduate work in physiology at the University of London in London, England, and the Kiel and Kaiser Wilhelm Institute in Berlin. Following this he did additional postgraduate work at the Hospital of the Rockefeller Institute in New York. Between 1926 and 1929, he was an Assistant in the Department of Pathology of Mount Sinai Hospital, New York. He was Chief of the Arthritis Clinic and a member of the Laboratory Research staff of Mount Sinai Hospital from 1927. From 1934 until 1939 he was Associate Visiting Physician, Harlem Hospital, New York. During 1941 he became an Officer of Instruction in Postgraduate Medicine, Columbia University College of Physicians and Surgeons.

Dr. Finkle was a Fellow of the New York Academy of Medicine, a Member of the New York County Medical Society, the Medical Society of the State of New York, the Harvey Society, the American Rheumatism Association, the American Medical Association, a Member of the Board of the Dazian Foundation for Medical Research since 1937, and he had been a Fellow of the American College of Physicians since 1940.

Dr. Finkle is survived by one brother and two sisters.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York